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(54) Title: SUBSTITUTED AMIDINOARYL DERIVATIVES AND THEIR USE AS ANTICOAGULANTS

(57) Abstract

The present invention relates to novel biheterocyclic derivatives which are factor Xa inhibitors; the pharmaceutically acceptable salts and *N*-oxides thereof; their uses as therapeutic agents and the methods of their making.

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SUBSTITUTED AMIDINOARYL DERIVATIVES AND THEIR USE AS ANTICOAGULANTS

This application is based on U.S. Provisional Application Serial Number 60/066,819 filed on November 26,1997.

THE INVENTION

This application relates to compounds and compositions for treating diseases associated with serine protease activity, particularly factor Xa activity.

DESCRIPTION OF THE FIELD

Hemostasis is a function of the physiological processes which initiate and modulate blood coagulation and fibrinolysis. Blood coagulation involves a series of highly complex, inter-related proteolytic events which culminate in the formation of a fibrin clot surrounding the platelet aggregate which makes up the primary hemostatic plug that forms to prevent loss of blood when a vessel is damaged. Fibrin is the product of a proteolytic reaction catalyzed by thrombin, a serine protease, which in turn is the product of a proteolytic activation of prothrombin by factor Xa, also a serine protease. Thrombin also is a potent activator of platelet aggregation.

Factor Xa is converted from inactive factor X by two distinct mechanisms referred to as the intrinsic and extrinsic coagulation pathways. The intrinsic pathway comprises a series of proteolytic reactions catalyzed by factors originating in blood and culminates in the formation of factor IXa. The extrinsic pathway comprises the activation of factor VII by tissue factor, a membrane bound protein, which is available at the site of vessel injury and culminates in the formation of factor VIIa. Factor IXa and factor VIIa, in consert with tissue factor, catalyzes the conversion of factor X to factor Xa. Thus, the formation of factor Xa represents a convergence of the entrinsic and extrinsic pathways in the cascade of events which lead to blood coagulation.

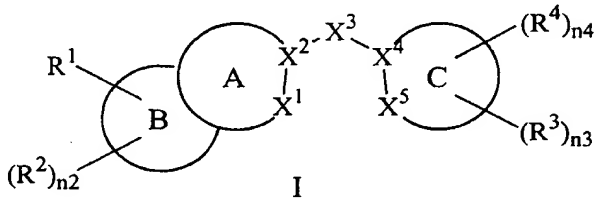
Fibrinolysis is the mechanism by which the platelet aggregate and fibrin clot is dissolved after the vessel injury has healed. The normal physiological condition results in an equilibrium between blood coagulation and anticoagulation mechanisms preventing hemorrhage while maintaining blood fluidity. A pathological condition leading to the occlusion of a blood vessel, i.e., thrombosis, is the equilibrium tipped in the direction of procoagulation. Arterial thrombosis which deprives tissue of oxygen will result in ischemic

necrosis of that tissue. Venous thrombosis may result in a pulmonary embolism. Agents which shift the equilibrium towards anticoagulation provide a method for treating and/or preventing thrombosis. Agents which inhibit factor Xa provide a valid pharmacological mechanism for effecting anticoagulation.

The disclosures of these and other documents referred to throughout this application are incorporated herein by reference.

SUMMARY OF THE INVENTION

This application relates to a compound of Formula I:



I

in which:

n2 is 1, 2 or 3;

n3 is 1, 2, 3 or 4;

n4 is 1 or 2;

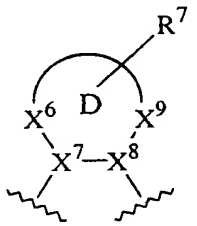
A together with B comprises a fused heterobicyclic radical containing 8 to 12 annular atoms, wherein each ring contains 5 to 7 annular members, each annular atom optionally is a heteroatom, X^1 and X^2 are adjacent annular members of an aromatic ring and X^1 is a heteroatom moiety selected from –N=, –NR^5–, –O– and –S–, wherein R^5 is –R^6 or –X^6–R^6, wherein X^6 is a linking group containing 1 to 12 contiguous linking atoms and R^6 is hydrogen, (C_{6-14})aryl, cyclo(C_{3-14})alkyl, hetero(C_{5-14})aryl, heterocyclo(C_{3-14})alkyl, hetero(C_{8-14})polycycloaryl or (C_{9-14})polycycloaryl;

C comprises a heteromonocyclic or fused heteropolycyclic radical containing 5 to 18 annular atoms, wherein each ring contains 5 to 7 annular members, each annular atom optionally is a heteroatom, X^4 and X^5 are adjacent annular members of an aromatic ring and X^5 is a heteroatom moiety selected from –N=, –NR^5–, –O– and –S–, wherein R^5 is as defined

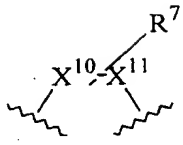
above, and any carbocyclic

ketone, thioketone and iminoketone derivative thereof;

X^3 represents a linking group of Formula (a) or (b):



(a)



(b)

in which D comprises a monocyclic or polycyclic divalent radical containing 5 to 10 annular atoms, wherein X^6, X^7, X^8 and X^9 are contiguous annular carbon atoms and one or more other annular atoms optionally is a heteroatom moiety heteroatom moiety selected from –N=, $-NR^5-$, –O– and –S–, wherein R^5 is as defined above, X^{10} and X^{11} together represent a linking group containing two contiguous linking atoms and R^7 is $-R^6$ or $-X^6-R^6$, wherein X^6 and R^6 are as defined above, with the proviso that when X^3 is a linking group of Formula (b) and R^7 is $-R^6$, wherein R^6 is substituted or unsubstituted heteroaryl or heteropolycycloaryl, then the annular atom of R^6 to which X^{10} or X^{11} is attached is not adjacent to an annular heteroatom moiety;

R^1 is amidino and bonded to any annular carbon atom with an available valence comprising B;

each R^2 is independently hydrogen, (C_{1-3})alkyl, (C_{1-3})alkyloxy, (C_{1-3})alkylsulfonyl, (C_{1-3})alkylthio, carboxy, halo, (C_{2-12})heteroalkyl, hydroxy, mercapto or nitro and bonded to any annular atom with an available valence comprising B;

each R^3 is independently hydrogen, cyano, halo, nitro, perhalo(C_{1-3})alkyl or perhalo(C_{1-3})alkyloxy and bonded to any annular atom with an available valence comprising C; and

each R^4 is independently $-R^6$ or $-X^6-R^6$, wherein X^6 and R^6 are as defined above, and bonded to any annular atom with an available valence comprising C;

wherein aliphatic or alicyclic moieties with an available valence comprising each X^6 and R^6 optionally are substituted with 1 to 5 substituents independently selected from (C_{1-6})alkyl, (C_{1-6})alkylamino, di(C_{1-6})alkylamino, (C_{1-6})alkylcarbamoyl, di(C_{1-6})alkylcarbamoyl, (C_{1-6})alkyloxy, (C_{1-6})alkyloxycarbonyl, (C_{1-6})alkylsulfinyl, (C_{1-6})alkylsulfonyl, (C_{1-6})alkylthio, amino, carbamoyl, carboxy, cyano, guanidino, halo, hydroxy, mercapto, perhalo(C_{1-3})alkyl, perhalo(C_{1-3})alkyloxy and uriedo; and aromatic moieties with an available valence comprising each X^6 and R^6 optionally are substituted with one to three substituents independently selected from (C_{1-3})alkyl, (C_{1-3})alkylamino, di(C_{1-3})alkylamino, (C_{1-3})alkyloxy, (C_{1-3})alkyloxycarbonyl, (C_{1-3})alkylimino, amino, carboxy, cyano, guanidino, halo, hydroxy, perhalo(C_{1-3})alkyl and perhalo(C_{1-3})alkyloxy; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

A second aspect of this invention is a pharmaceutical composition which contains a compound of Formula I or a *N*-oxide derivative, prodrug derivative, individual isomer, mixture of isomers or pharmaceutically acceptable salt thereof in admixture with one or more suitable excipients.

A third aspect of this invention is a method of treating a disease in an animal in which contributes to the pathology and/or symptomatology of the disease, which method comprises administering to the animal a therapeutically effective amount of compound of Formula I or a *N*-oxide derivative, prodrug derivative, individual isomer, mixture of isomers or pharmaceutically acceptable salt thereof.

A fourth aspect of this invention is the processes for preparing compounds of Formula I and the *N*-oxide derivatives, prodrug derivative, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof as set forth in "Detailed Description of the Invention".

DETAILED DESCRIPTION OF THE INVENTION

Definitions:

Unless otherwise stated, the following terms used in the specification and claims have the meanings given in this Section:

"Alicyclic moiety" means any saturated or unsaturated, monocyclic or polycyclic portion of a radical and includes cycloalkyl, cycloalkylene, heterocycloalkyl and heterocycloalkylene, as defined in this Section. For example, alicyclic moiety refers to cycloalkyl as well as to the alicyclic portions comprising cycloalkylalkyl, cycloalkyloxy, cycloalkylcarbonyl, cycloalkylcarbamoyl, polycycloaryl, and the like.

"Aliphatic moiety" means any straight or branched, saturated or unsaturated portion of a radical and includes alkyl, alkylene, heteroalkyl and heteroalkylene, as defined in this Section. For example, aliphatic moiety refers to alkyl as well as to aliphatic portions comprising alkyloxy, arylalkyl, alkylcarbamoyl, and the like.

"Alkyl", for the purposes of this application, means a straight or branched, saturated or unsaturated aliphatic radical having the number of carbon atoms indicated, and any ketone, thioketone or iminoketone derivative thereof (e.g., (C_{1-6})alkyl includes methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, *tert*-butyl, vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methylallyl, ethynyl, 1-propynyl, 2-propynyl, 3-oxopentyl, 3-thioxopentyl, 3-iminopentyl, etc.).

"Alkylene" means a saturated or unsaturated divalent radical having the number of carbon atoms indicated and any ketone, thioketone, iminoketone and substituted derivative thereof (e.g., (C_{1-10})alkylene includes methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), methylethylene, vinylene, ethynylene, trimethylene ($-CH_2CH_2CH_2-$), 2-oxotrimethylene ($-CH_2C(O)CH_2-$), 2-thiatrimethylene ($-CH_2C(S)CH_2-$), 2-iminotrimethylene ($-CH_2C(NH)CH_2-$), propenylene ($-CH_2CH=CH-$ or $-CH=CHCH_2-$), propanylylidene ($=CHCH_2CH_2-$), propendiylene ($=CHCH=CH-$), 1-aminotetramethylene, pentamethylene, etc.).

"Alkyloxy" means the radical -OR, wherein R is alkyl as defined in this Section, having the number of carbon atoms indicated (e.g., (C_{1-6})alkyloxy includes the radicals methoxy, ethoxy, propoxy, isopropoxy, butoxy, *sec*-butoxy, isobutoxy, *tert*-butoxy, vinyloxy, allyloxy, 1-propenyloxy, isopropenyloxy, 1-butenyloxy, 2-butenyloxy, 3-butenyloxy, 2-methylallyloxy, ethynyloxy, 1-propynyloxy, 2-propynyloxy, etc.).

"Alkylsulfonyl" and "alkylthio" mean the radicals $-S(O)_2R$ and -SR, respectively, wherein R is alkyl as defined in this Section, having the number of carbon atoms indicated (e.g., (C_{1-6})alkylsulfonyl includes methylsulfonyl, ethylsulfonyl, propylsulfonyl,

isopropylsulfonyl, butylsulfonyl, *sec*-butylsulfonyl, isobutylsulfonyl, *tert*-butylsulfonyl, vinylsulfonyl, allylsulfonyl, 1-propenylsulfonyl, isopropenylsulfonyl, 1-butenylsulfonyl, 2-butenylsulfonyl, 3-butenylsulfonyl, 2-methylallylsulfonyl, ethynylsulfonyl, 1-propynylsulfonyl, 2-propynylsulfonyl, etc.).

"Amidino" means the radical $-C(NH)NH_2$.

"Amino" means the radical $-NH_2$.

"Animal" includes humans, non-human mammals (e.g., dogs, cats, rabbits, cattle, horses, sheep, goats, swine, deer, etc.) and non-mammals (e.g., birds, etc.).

"Aryl" means an aromatic monocyclic or fused polycyclic radical containing the number of annular carbon atoms indicated, wherein each ring contained therein is comprised of 6 annular members (e.g., (C_{6-14})aryl includes phenyl, naphthalenyl, anthracenyl, phenanthrenyl, etc.).

"Arylene" means an aromatic monocyclic or fused bicyclic divalent radical containing 6 to 10 annular atoms, wherein each ring contained therein is comprised of 6 annular members (e.g., arylene includes 1,4-phenylene, 1,2-phenylene, 1,5-naphthalenylene, 1,8-naphthaleylene, etc.).

"Aromatic moiety" means any aromatic portion of a radical and includes aryl and heteroaryl, as defined in this Section. For example, aromatic moiety refers to aryl as well as the aromatic portions comprising arylalkyl, polycycloaryl, and the like.

"Carbamoyl" means the radical $-C(O)NH_2$.

"Carboxy" means the radical -C(O)OH.

"Cyano" means the radical -CN.

"Cycloalkyl" means a saturated or unsaturated, monocyclic or fused polycyclic radical containing the number of annular carbon atoms indicated, wherein each ring contained therein is comprised of 3 to 8 annular members, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., (C_{3-14})cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, 2,5-cyclohexadienyl, bicyclo[2.2.2]octyl, oxocyclohexyl, dioxocyclohexyl, thiocyclohexyl, 2-oxobicyclo[2.2.1]hept-1-yl, 1-azabicyclo[2.2.2]oct-3-yl, etc.).

"Cycloalkylene" means a saturated or unsaturated, monocyclic or fused bicyclic divalent radical containing 3 to 14 annular atoms, wherein each ring contained therein is

comprised of 3 to 8 annular members, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., cycloalkylene includes cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene, cyclohexenylene, 2,5-cyclohexadienylene, bicyclo[2.2.2]octylene, oxocyclohexylene, dioxocyclohexylene, thiocyclohexylene, 2-oxobicyclo[2.2.1]hept-1-ylene, 1-azabicyclo[2.2.2]oct-3-ylene, etc.).

"Disease" specifically includes any unhealthy condition of an animal or part thereof and includes an unhealthy condition which may be caused by, or incident to, medical or veterinary therapy applied to that animal, i.e., the "side effects" of such therapy.

"Fused heteropolycyclic radical" includes "fused heterobicyclic radical" and means a heterocyclic radical containing two or more rings having the number of annular members indicated, wherein at least two annular members of one ring are common to a second ring (e.g., a heteropolycyclic radical containing from 5 to 18 annular atoms and the carbocyclic ketone and thioketone derivatives thereof includes 1*H*-benzimidazol-2-yl, 1*H*-naphtho[2,3-*d*]imidazol-2-yl, 1*H*-imidazo[4,5-*f*]quinolin-2-yl, 1*H*-imidazo[4,5-*b*]pyridin-2-yl, 1*H*-phenanthro[9,10-*d*]imidazol-2-yl, 1*H*-imidazo[4,5-*g*]quinoxalin-2-yl, 2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl, 2,6-dithioxo-2,3,6,9-tetrahydro-1*H*-purin-8-yl, 7*H*-purin-8-yl, 1,6-dihydrocyclopentaimidazol-2-yl, 4-quinolin-2-yl, etc.)

"Guanidino" means the radical $-NHC(NH)NH_2$.

"Halo" means fluoro, chloro, bromo or iodo.

"Heteroatom" means an atom selected from N, O, S and P.

"Heteroatom moiety", unless indicated otherwise, means a moiety selected from $-N=$, $-NR^8-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-P(O)(OR^8)-$, wherein R^8 is hydrogen or (C_{1-6})alkyl.

"Heteroalkyl" means alkyl, as defined in this Section, except one or more of the carbon atoms indicated is replaced by a heteroatom moiety, as defined in this Section, and any ketone, thioketone or iminoketone derivative thereof (e.g., hetero(C_{2-12})alkyl includes methoxy, ethoxy, ethylthio, 2-(2-methoxyethoxy)ethoxy, 3-methoxymethoxycarbonylmethoxy, 2-(*N*-ethyl-*N*-methylamino)ethyl, 2-ethyliminoethyl, ethoxymethoxyphosphoryloxy, etc.).

"Heteroalkylene" means alkylene, as defined in this Section, except one or more of the carbon atoms indicated is replaced by a heteroatom moiety, as defined in this Section, or

any suitable combination thereof (e.g., $-OS(O)_2-$, $-S(O)_2O-$, $-N(R^8)S(O)_2-$, $-S(O)_2NR^8-$, $-OP(O)(OR^8)O-$, and the like, wherein R^8 is hydrogen or (C_{1-6})alkyl), and any ketone, thioketone or iminoketone derivative thereof (e.g., hetero(C_{2-10})alkylene includes azaethylene ($-CH_2NH-$), 2-azapropenylene ($-CH_2N{=}CH_2-$), 1-oxatrimethylene ($-CH_2CH_2O-$), 2-oxo-3-azapentamethylene, 3-aza-2-thiopentamethylene, 2-oxa-3-oxopentamethylene, 3-aza-2-iminopentamethylene ($-CH_2CH_2NHC(NH)CH_2-$), 2,4-aza-2-methyl-3,3-dioxo-3-thiapentamethylene ($-CH_2NHS(O)_2N(CH_3)CH_2-$), 3-hydroxy-2,4-oxa-3-oxo-3-phosphapentamethylene ($-CH_2OP(O)(OH)OCH_2-$), 3-aza-2-oxo-4-carboxyhexamethylene, 4-aza-1-oxa-3-oxohexamethylene, 1-thia-3-oxo-4-azahexamethylene, 1-thia-1,1,3-trioxo-4-azahexamethylene ($-CH_2CH_2NHC(O)CH_2S(O)_2-$), 3-aza-4-oxoheptamethylene, 1,4,7-trioxaoctamethylene, 6-aza-1-oxa-2,5-dioxooctamethylene ($-CH_2CH_2NHC(O)CH_2CH_2C(O)O-$), 3-aza-4-oxodecamethylene, etc.).

"Heteroaryl" means an aromatic monocyclic or fused polycyclic divalent radical having the number of annular atoms indicated, wherein each ring contained therein is comprised of 5 to 6 annular members and one or more of the annular atoms is a heteroatom moiety selected from $-N{=}$, $-NR^8-$, $-O-$ or $-S-$, and each ring contained therein is comprised of 5 to 6 annular members (e.g., hetero(C_{5-14})aryl includes thienyl, furyl, pyrrolyl, pyrimidinyl, isoxazolyl, oxaxolyl, indolyl, benzo[*b*]thienyl, isobenzofuranyl, purinyl, isoquinolyl, pterdinyl, perimidinyl, imidazolyl, pyridyl, pyrazolyl, pyrazinyl, quinolyl, etc.).

"Heteroarylene" means an aromatic monocyclic or fused bicyclic divalent radical containing 5 to 10 annular atoms, wherein each ring contained therein is comprised of 5 to 6 annular members and one or more of the annular atoms is a heteroatom moiety selected from $-N{=}$, $-NR^8-$, $-O-$ or $-S-$, (e.g., heteroaryl includes thienylene, furylene, pyrrolylene, pyrimidinylene, isoxazolylene, oxaxolylene, indolylene, benzo[*b*]thienylene, isobenzofuranylene, purinylene, isoquinolylene, imidazolylene, pyridylene, pyrazolylene, pyrazinylene, quinolylene, etc.).

"Heterocycloalkyl" means cycloalkyl, as defined in this Section, except one or more of the annular carbon atoms indicated are replaced by a heteroatom moiety, as defined in this Section, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., the term heterocyclo(C_{5-14})alkyl includes piperidyl, pyrrolidinyl, pyrrolinyl,

imidazolidinyl, quinuclidinyl, morpholinyl, etc.).

"Heterocycloalkylene" means cycloalkylene, as defined in this Section, except one or more of the annular carbon atoms indicated is replaced by a heteroatom moiety, as defined in this Section, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., the term heterocyclo(C_{3-14})alkylene includes piperidylene, pyrrolidinylene, pyrrolinylene, imidazolidinylene, quinuclidinylene, morpholinylene, etc.).

"Heteropolycycloaryl" means polycycloaryl, as defined below, except one or more of the annular carbon atoms indicated are replaced by a heteroatom moiety, as set defined in the Detailed Description of the Invention, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., heteropolycyclo(C_{8-10})alkyl includes 3,4-dihydro-2*H*-quinolinyl, 5,6,7,8-tetrahydroquinolinyl, 3,4-dihydro-2*H*-[1,8]naphthyridinyl, 2,4-dioxo-3,4-dihydro-2*H*-quinazolinyl, 3-oxo-2,3-dihydrobenzo[1,4]oxazinyl, etc.).

"Heteropolycycloarylene" means polycycloarylene, as defined below, except one or more of the annular carbon atoms indicated is replaced by a heteroatom moiety, as set defined in the Detailed Description of the Invention, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., heteropolycyclo(C_{8-10})alkylene includes 3,4-dihydro-2*H*-quinolinylene, 5,6,7,8-tetrahydroquinolinylene, 3,4-dihydro-2*H*-[1,8]naphthyridinylene, 2,4-dioxo-3,4-dihydro-2*H*-quinazolinylene, 3-oxo-2,3-dihydrobenzo[1,4]oxazinylene, etc.).

"Hydroxy" means the radical -OH.

"Imino" means the radical =NH.

"Iminoketone derivative" refers to a radical containing the moiety –C(NR)–, wherein R is hydrogen or (C_{1-6})alkyl.

"Isomers" mean compounds of Formula I having identical molecular formulae but differ in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "steroisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and stereoisomers that are nonsuperimposable mirror images are termed "enantiomers" or sometimes "optical isomers". A carbon atom bonded to four nonidentical substituents is termed a "chiral center". A compound with one chiral center has two

enantiomeric forms of opposite chirality is termed a "racemic mixture". A compound that has more than one chiral center has 2^{n-1} enantiomeric pairs, where n is the number of chiral centers. Compounds with more than one chiral center may exist as ether an individual diasteromer or as a mixture of diastereomers, termed a "diastereomeric mixture". When one chiral center is present a stereoisomer may be characterized by the absolute configuration of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. Enantiomers are characterized by the absolute configuration of their chiral centers and described by the *R*- and *S*-sequencing rules of Cahn, Ingold and Prelog. Conventions for stereochemical nomenclature, methods for the determination of stereochemistry and the separation of stereoisomers are well known in the art (e.g., see "Advanced Organic Chemistry", 3rd edition, March, Jerry, John Wiley & Sons, New York, 1985). It is understood that the names and illustration used in this application to describe compounds of Formula I are meant to be encompassed all possible stereoisomers. Thus, for example, compounds of Formula I in which R^4 is 1-carboxy-2-methylpropylcarbamoyl contains a chiral center and can exist as the (*R*)- or (*S*)-isomer or a mixture thereof, racemic or otherwise. For the purposes of the present application when referring to a compound of Formula I by name or by formula and the configuration is designated, it is to be understood that the reference is to all possible configurations of the compound.

"Ketone derivative" refers to a radical containing the moiety -C(O)-.

"Leaving group" has the meaning conventionally associated with it in synthetic organic chemistry, i.e., an atom or group displaceable under alkylating conditions, and includes, halogen, hydroxy, alkyloxy, alkylsulfonloxy (e.g., mesyloxy, ethanesulfonyloxy, etc.), arylsulfonyloxy (e.g., benzenesulfonyloxy and tosyloxy, thienyloxy), dihalophosphinoyloxy, tetrahalophosphaoxy, and the like.

"Linking group" means a saturated or unsaturated divalent radical having the number of contiguous linking atoms indicated, wherein "contiguous linking atoms" refers to the minimum number of connecting atoms linking the free valences, and any substituted, ketone, thioketone or iminoketone derivative thereof. The linking group may contain one or more heteroatom moieties, as defined in this Section, one or more suitable combinations of heteroatom moieties (e.g., $-OS(O)_2-$, $-S(O)_2O-$, $-N(R^8)S(O)_2-$, $-S(O)_2NR^8-$,

$-OP(O)(OR^8)O-$, etc.), alkylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, heteroarylene, polycycloarylene, heteropolycycloarylene, and any combination and carbocyclic ketone, thioketone and iminoketone derivative thereof (e.g., $-C(O)-$, $-C(O)O-$, $-OC(O)-$, $-N(R^8)C(O)-$, $-C(O)NR^8-$, $-N(R^8)C(O)O-$, $-OC(O)NR^8-$, $-N(R^8)C(O)NR^8-$, $-N(R^8)C(N)-$, etc.). Hence, a linking group containing 1 to 12 contiguous linking atoms may include one or more heteroatom moieties, one or more suitable combinations of heteroatom moieties and one or more groups selected from (C_{2-10})alkylene, hetero(C_{2-10})alkylene, cycloalkylene, heterocycloalkylene, arylene, heteroarylene, polycycloarylene and heteropolycycloarylene, and any combination thereof (e.g., methylenephen-1,4-ylene ($-C_6H_4CH_2-$ or $-CH_2C_6H_4-$), methylenepiperazin-1,4-ylene ($-N_2C_4H_8CH_2-$ or $-CH_2N_2C_4H_8-$), methyleneoxaphen-1,4-ylene ($-OC_6H_4CH_2-$ or $-CH_2C_6H_4O-$), etc.).

"Mercapto" means the radical -SH.

"Nitro" means the radical $-NO_2$.

"Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, the phrase "optionally are substituted with one to three radicals" means that the group referred to may or may not be substituted in order to fall within the scope of the invention.

"*N*-oxide derivatives" means a derivatives of compound of Formula I in which nitrogens are in an oxidized state (i.e., O←N) and which possess the desired pharmacological activity.

"Pathology" of a disease means the essential nature, causes and development of the disease as well as the structural and functional changes that result from the disease processes.

"Pharmaceutically acceptable" means that which is userul in preparing a pharmaceutical composition that is generall safe, non-toxic and neither biologically nor otherwise undesirabale and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Perhalo(C_{1-3})alkyl" means alkyl, as defined in this Section, except all of the hydrogen atoms are replaced by haloatoms (e.g., trifluoromethyl, etc.).

"Pharmaceutically acceptable salts" means salts of compounds of Formula I which are pharmaceutically acceptable, as defined in this Section, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartatic acid, citric acid, benzoic acid, *o*-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, madelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, *p*-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic aicd, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid and the like.

Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydoxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine and the like.

"Polycycloaryl" means a fused polycyclic radical containing the number of annular carbon atoms indicated, wherein at least one, but not all, of the fused rings comprising the radical is aromatic and each ring contained therein is comprised of 5 to 6 annular members, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., polycyclo(C_{9-10})aryl includes indanyl, indenyl, 1,2,3,4-tetrahydronaphthalenyl, 1,2-dihydronaphthalenyl, 2,4-dioxo-1,2,3,4-tetrahydronaphthalenyl, etc.).

"Polycycloarylene" means a fused bicyclic divalent radical containing 10 to 12 annular atoms, wherein at least one, but not both, of the fused rings comprising the radical is aromatic and each ring contained therein is comprised of 5 to 6 annular members, and any carbocyclic ketone, thioketone or iminoketone derivative thereof

(e.g., polycyclo(C_{9-10})arylene includes indanylene, indenylene, 1,2,3,4-tetrahydronaphthalenylene, 1,2-dihydronaphthalenylene, 2,4-dioxo-1,2,3,4-tetrahydronaphthalenylene, etc.).

"Prodrug derivatives" means derivatives of compounds of Formula I which are converted *in vivo* to the corresponding non-derivatized form of a compound of Formula I. For example, suitable prodrug derivatives include compounds of Formula I wherein the R^1 amidino group is hydroxy- or (C_{1-6})alkyloxy-substituted.

"Protected derivatives" means derivatives of compounds of Formula I in which a reactive site or sites are blocked with protective groups. Protected derivatives of compounds of Formula I are useful in the preparation of compounds of Formula I or in themselves may be active inhibitors of factor Xa. For example, a compound of Formula I may have one or more reactive amino groups. Suitable protecting groups for reactive nitrogen atoms include acetyl, *tert*-butoxycarbonyl, benzyloxycarbonyl and any other suitable amino protective groups (e.g., see T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1981).

"Therapeutically effective amount" means that amount which, when administered to an animal for treating a disease, is sufficient to effect such treatment for the disease.

"Thioketone derivative" refers to a radical containing the moiety -C(S)-.

"Treatment" or "treating" refers to any administration of a compound of the present invention and includes:

(1) preventing the disease from occurring in an animal which may be predisposed to the disease but does not yet experience or display the pathology or symptomatology of the disease,

(2) inhibiting the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., arresting further development of the pathology and/or symptomatology), or

(3) amelorating the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., reversing the pathology and/or symptomatology).

"Sulfo" means the radical -S(O)OH.

"Uriedo" means the radical $-NHC(O)NH_2$.

The compounds of Formula I and the intermediates and starting materials used in

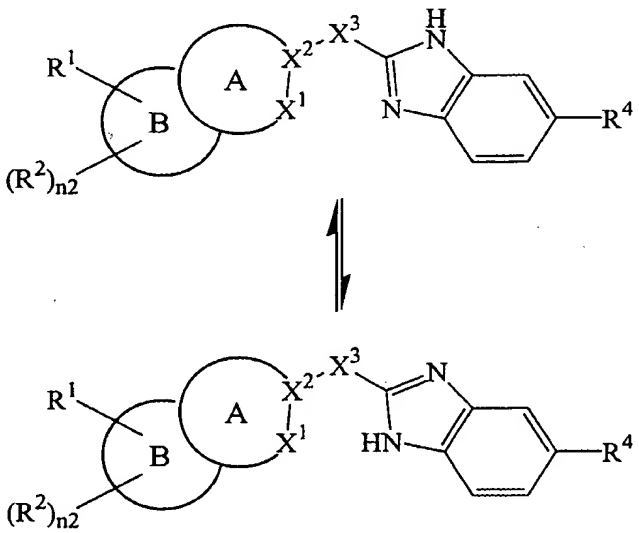
their preparation are named in accordance with IUPAC rules of nomenclature in which the characteristic groups have decreasing priority for citation as the principle group as follows: acids, esters, amides and amidines. For example, a compound of Formula I in which:

A together with B comprises 5-amidino-1*H*-benzimidazol-2-yl, C comprises 6-methoxycarbonyl-1-methyl-1*H*-benzimidazol-2-yl and X^3 is ethylene is named methyl 2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-3-methyl-3*H*-benzimidazole-5-carboxylate;

A together with B comprises 5-amidino-1*H*-benzimidazol-2-yl, C comprises 5-(4-aminophenoxy)-1*H*-benzimidazol-2-yl and X^3 is ethylene is named 2-[2-(5-(4-aminophenoxy)-1-*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazole-5-carboxamidine; and

A together with B comprises 5-amidino-1*H*-benzimidazol-2-yl, C comprises 1*H*-benzimidazol-2-yl and X^3 is ethylene is named 2-{2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazol-5-ylcarbonylamino}-3-methylbutyric acid.

Certain compounds of Formula I exist in tautomeric equilibrium. For example, compounds of Formula I in which C comprise a 1*H*-imidazol-2-yl exist in equilibrium between tautomers of the following formulae:



wherein R^4 is not hydrogen. Compounds of Formula I which exist as tautomers are named, illustrated or otherwise described in this application as one possible tautomer. However, it

is to be understood that the all possible tautomers are meant to be encompassed by such names, illustrations and descriptions. Thus, the name 2-[2-(5-chloro-1*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazole-5-carboxamidine is meant to include its tautomers 2-[2-(6-chloro-1*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazole-5-carboxamidine, 2-[2-(6-chloro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole-5-carboxamidine and 2-[2-(5-chloro-1*H*-benzimidazol-2-yl)ethyl]-

3*H*-benzimidazole-5-carboxamidine.

Presently Preferred Embodiments:

While the broadest definition of this Invention is set forth in the Summary of the Invention, certain aspects of the Invention are preferred. A preferred aspect of the Invention are compounds of Formula I in which:

n2 is 1;

A together with B comprises a fused heterobicyclic radical containing 8 to 10 annular atoms, wherein each ring contains 5 to 6 annular members;

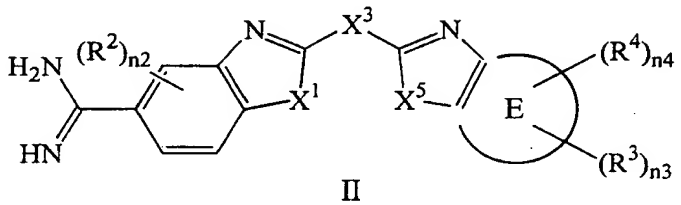
C comprises a fused heteropolycyclic radical containing from 9 to 13 annular atoms, wherein each ring contains 5 to 6 annular atoms;

X^3 represents a linking group of Formula (a) or (b) in which D comprises a monocyclic divalent radical containing 6 annular carbon atoms;

each R^3 is independently hydrogen, halo or hydroxy; and

each R^4, R^5 and R^7 is independently $-R^6$ or $-X^6-R^6$, wherein X^6 is a linking group containing 1 to 10 contiguous linking atoms and R^6 is hydrogen, (C_{6-10})aryl, cyclo(C_{3-6})alkyl, hetero(C_{5-10})aryl, heterocyclo(C_{5-6})alkyl or hetero(C_{8-10})polycycloaryl.

A further preferred aspect of the Invention is a compound of Formula II:



II

in which E together with the vinylene moiety to which it is fused comprises a monocyclic or heteromonocyclic divalent radical containing 6 annular atoms; X^3 is ethylene, carbamoylethylene, methoxycarbonylethylene, *trans*-1,2-methylvinylene, 1,2-phenylene or 1-cyclohexen-1,2-ylene; and X^1 and X^5 are independently a heteroatom moiety selected from $-NR^5-$, -O- and -S-.

A further preferred aspect of the Invention is a compound of Formula II in which each R^4, R^5 and/or R^7 is independently $-R^6$, wherein R^6 is (C_{6-14})aryl, cyclo(C_{3-14})alkyl, hetero(C_{5-14})aryl, heterocyclo(C_{3-14})alkyl, hetero(C_{8-14})polycycloaryl or (C_{9-14})polycycloaryl, or $-X^6-R^6$, wherein X^6 is (C_{1-10})alkylene, or (C_{2-10})heteroalkylene and R^6 is hydrogen, (C_{6-14})aryl, cyclo(C_{3-14})alkyl, hetero(C_{5-14})aryl, heterocyclo(C_{3-14})alkyl, hetero(C_{8-14})polycycloaryl or (C_{9-14})polycycloaryl.

A further preferred aspect of the Invention is a compound of Formula II in which each R^3 is independently cyano, halo, nitro, perhalo(C_{1-3})alkyl or perhalo(C_{1-3})alkyloxy and/or each R^4 is independently hydroxy, mercapto, sulfo, $-NHR^8$ or $-OP(O)(OR^8)OH$, wherein R^8 is hydrogen or (C_{1-6})alkyl.

A further preferred aspect of the Invention is a compound of Formula II in which one of X^1 and X^5 is $-NR^5-$ and the other is a heteroatom selected from -O- and -S-; in particular, compounds of Formula II wherein X^1 is -S- and X^5 is $-NR^5-$.

Further preferred are the following compounds of Formula I:

methyl 2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-3-methyl-3*H*-benzimidazole-5-carboxylate;

2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-*N*-benzyl-3*H*-benzimidazole-5-carboxamide;

3-(5-amidino-1*H*-benzimidazol-2-yl)-2-(1*H*-benzimidazol-2-yl)propionamide;

2-[2-(5-imidazol-1-yl-1-*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazole-5-carboxamidine;

2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-3-methyl-3*H*-benzimidazole-5-carboxylic acid;

2-[2-(1-benzyl-1*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazole-5-carboxamidine;

2-[2-(1*H*-benzimidazol-2-yl)ethyl]-3-(3-phenylpropyl)-3*H*-benzimidazole-5-carboxamidine;

2-{2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazol-5-ylcarbonylamino}-3-methylbutyric acid;

2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazole-5-carboxylic acid;

2-{2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazol-5-ylcarbonylamino}pentandioic acid;

6-amino-2-{2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazol-5-ylcarbonylamino}-3-methylhexanoic acid;

2-{2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazol-5-ylcarbonylamino}propionic acid; and

2-{2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazol-5-ylcarbonylamino}-3-phenylpropionic acid.

Pharmacology and Utility:

The compounds of this invention are factor Xa inhibitors and, as such, are useful for treating diseases in which factor Xa activity contributes to the pathology and/or symptomatology of the disease. Uses for factor Xa inhibitors include therapy in treating venous thromboembolism (obstruction of a blood vessel with thrombotic material carried by the blood stream from the site of origin to plug another vessel), to reduce the risk of myocardial infarction in patients with unstable angina, to ameliorate further loss of cardiac function in patients with acute myocardial infarction, to reduce the risk of occlusion of saphenous grafts, to reduce periprocedural thrombosis in patients undergoing angioplasty procedures, to reduce the risk of ischemic stroke in patients with atrial fibrillation, to reduce the risk of embolism associated with mechanical heart valves and valvular heart disease, to

prevent ischemic strokes in patients with cerebrovascular atherosclerosis, in patients with peripheral vascular disease, and the like.

Suitable *in vitro* assays for measuring factor Xa activity and the inhibition thereof by test compounds are known. Typically, the assay measures factor Xa induced hydrolysis of a peptide base substrate. Suitable *in vivo* and *ex vivo* models for measuring the anti-coagulation activity of test compounds are known to those of ordinary skill in the art. For further details of the assays for measuring factor Xa inhibitor and/or anticoagulant activity see Examples 17, 18 and 19, infra.

Administration and Pharmaceutical Compositions:

In general, compounds of Formula I will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with another therapeutic agent. A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. For example, therapeutically effective amounts of a compound of Formula I for anticoagulant therapy may range from 0.1 micrograms per kilogram body weight (μg/kg) per day to 1 milligram per kilogram body weight (mg/kg) per day, typically 1 μg/kg/day to 0.1 mg/kg/day. Therefore, a therapeutically effective amount for a 80 kg human patient may range from 10 μg/day to 10 mg/day, typically 0.1 mg/day to 10 mg/day. In general, one of ordinary skill in the art, acting in reliance upon personal knowledge and the disclosure of this application, will be able to ascertain a therapeutically effective amount of a compound of Formula I for treating a given disease.

The compounds of Formula I can be administered as pharmaceutical compositions by one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository) or parenteral (e.g., intramuscular, intravenous or subcutaneous). Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate composition and are comprised of, in general, a compound of Formula I in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the active ingredient.

Such excipient may be any solid, liquid, semisolid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

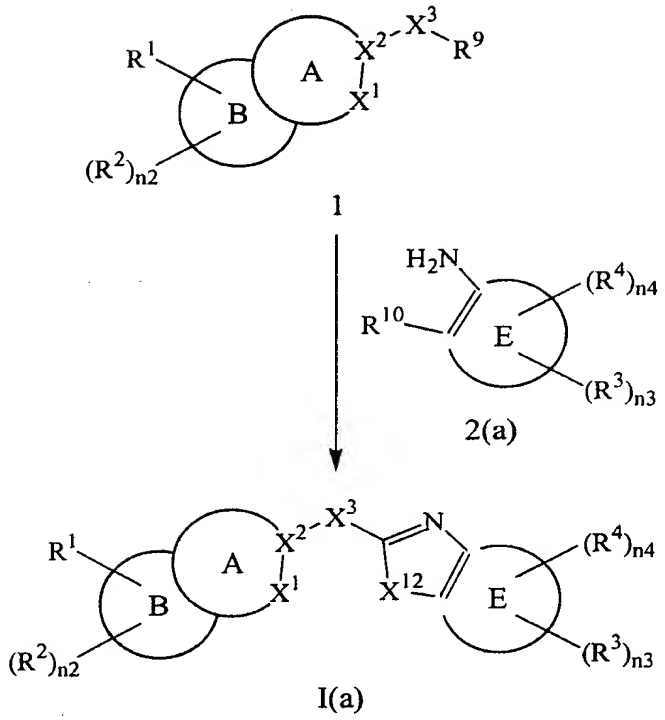
Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, and the like. Liquid and semisolid excipients may be selected from water, ethanol, glycerol, propylene glycol and various oils, including those of petroleum, animal, vegetable or synthetic origin (e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc.). Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose and glycols.

The amount of a compound of Formula I in the composition may vary widely depending upon the type of formulation, size of a unit dosage, kind of excipients and other factors known to those of skill in the art of pharmaceutical sciences. In general, a composition of a compound of Formula I for treating a given disease will comprise from 0.01%w to 10%w, preferably 0.3%w to 1%w, of active ingredient with the remainder being the excipient or excipients. Preferably the pharmaceutical composition is administered in a single unit dosage form for continuous treatment or in a single unit dosage form ad libitum when relief of symptoms is specifically required. Representative pharmaceutical formulations containing a compound of Formula I are described in Example .

Chemistry:

Compounds of Formula I in which X^4 and X^5 are adjacent members of an oxazol-2-yl, 1*H*-imidazol-2-yl or thiazol-2-yl ring and C comprises a fused polycyclic radical can be prepared by the methods depicted in the following reaction scheme:

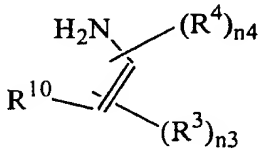
Scheme 1



in which R^9 is -C(O)L or -CN, wherein L is a leaving group, E together with the vinylene moiety to which it is fused comprises a monocyclic or fused bicyclic divalent radical containing from 5 to 15 annular atoms, wherein each ring contains 5 to 7 annular atoms and optionally one or more annular members is a heteroatom moiety, X^{12} is -O-, -N(R^5)- or -S -, R^{10} is -OH, -NHR^5 or -SH and heteroatom moiety, n2, n3, n4, A, B, X^1, X^2, X^3, R^1, R^2, R^3, R^4 and R^5 are as defined in the Summary of the Invention.

Compounds of Formula I in which X^4 and X^5 are adjacent members of an oxazol-2-yl, 1*H*-imidazol-2-yl or thiazol-2-yl ring comprising a fused polycyclic radical (Formula I(a)) can be prepared by reacting a compound of Formula 1 with a compound of Formula 2(a). The reaction may be carried out neat, but preferably is carried out in the presence of 1,3-dimethyl-3, 4, 5, 6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) or polyphosphoric acid, at 160 to 200 °C, preferably 170-180 °C, and requires 2 to 3 hours to complete (e.g., see Examples 3 and 4, infra.). Compounds of Formula I in which C comprises oxazol-2-yl, 1*H*-imdazol-2-yl or thiazol-2-yl can be prepared by proceeding as in

Scheme I, but replacing the compound of Formula 2(a) with a compound of Formula 2(b):

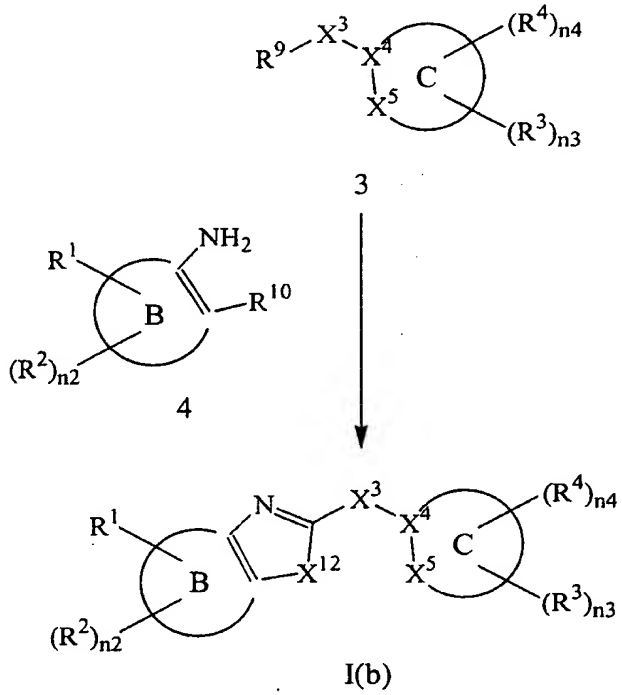


2(b)

in which R^{10} is –OH, –NHR^5 or –SH and each p, q, R^3, R^4 and R^5 is as defined in the Summary of the Invention.

In a similar fashion, compounds of Formula I in which X^1 and X^2 are adjacent members of an oxazol-2-yl, 1*H*-imidazol-2-yl or thiazol-2-yl ring can be prepared by the methods depicted in the following reaction scheme:

Scheme 2



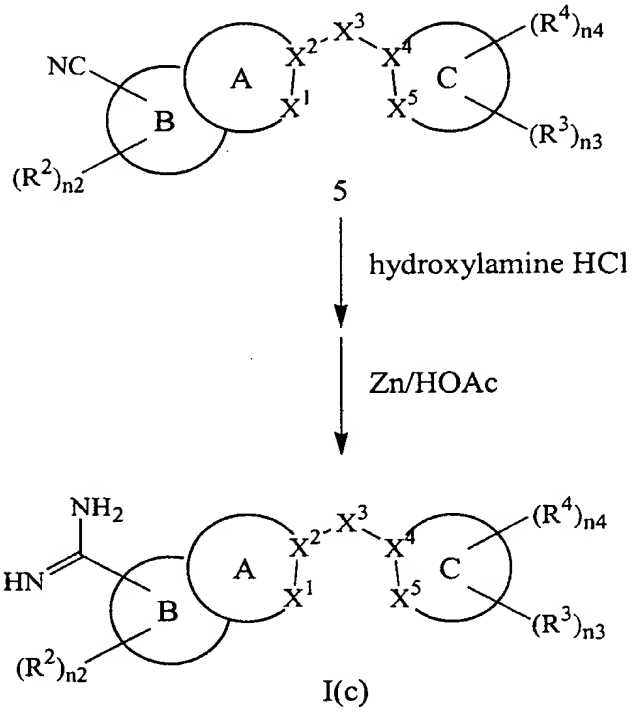
I(b)

in which R^9 is –C(O)L or –CN, wherein L is a leaving group, X^{12} is $N(R^5)$, O or S, R^{10} is –OH, –NHR^5 or –SH and n2, n3, n4, B, C, X^3, X^4, X^5, R^1, R^2, R^3, R^4 and R^5 are as defined in

the Summary of the Invention (e.g., see Example 5, infra.).

Compounds of Formula I can be prepared by the methods depicted in the following reaction scheme:

Scheme 3

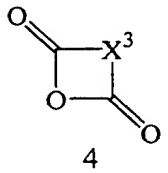


in which n2, n3, n4, A, B, C, X^1, X^2, X^3, X^4, X^5, R^2, R^3, R^4 and R^5 are as defined in the Summary of the Invention.

Compounds of Formula I can be prepared by reacting a corresponding nitrile with hydroxylamine hydrochloride to give a *N*-hydroxy amidine and then dehydroxylating to give the unsubstituted amidine. The reaction with the hydroxylamine may be carried out in the presence of sodium bicarbonate and in a suitable solvent (e.g., ethanol) at reflux temperature and requires 12 to 18 hours. The dehydroxylation can be effected by reacting the *N*-hydroxy amidine with zinc in the presence of acetic acid at reflux temperature and requires 3 to 4 hours to complete.

In general, the starting materials required for preparing the compounds of Formula I are either commercially available or can be readily prepared by methods known to those of

ordinary skill in the art or as described herein. For example, compounds of Formula 1 or Formula 3 in which L is hydroxy and X^1 and X^2 or X^4 and X^5 are adjacent members of an oxazole, imidazole or thiazole ring can be prepared by reacting an appropriate compound of Formula 4 or Formula 2, respectively, with an anhydride of Formula 4:



4

in which X^3 is as defined in the Summary of the Invention (e.g., dihydrofuran-2,5-dione, furan-2,5-dione, 3,4-dimethylfuran-2,5-dione, isobenzofuran-1,3-dione, 4,5,6,7-tetrahydroisobenzofuran-1,3-dione, etc.). The reaction is carried out in a suitable solvent (e.g., acetic acid, etc.) 80 to 100° C, and requires 6 to 10 hours (for further details see Example 1, infra.).

Compounds of Formula 2(a) in which R^4 is -OR, -NRR' or -SR, wherein R and R' are independent or together with the nitrogen atom to which they are attached form heterocycloalkyl, can be prepared by reacting a correspondingly appropriate amine, alcohol, thiol or heterocycloalkane with a corresponding halo-subsituted nitroaniline and then reducing. The reaction with the halo-substituted nitroaniline typically is carried out in a suitable solvent (e.g., THF) at 25 to 60 °C and requires 4 to 5 hours to complete.

Additional procedures:

Compounds of Formula I in which R^4, R^5 or R^7 comprises $-X^{13}C(O)NR^8X^{14}R^6$ can be prepared by reacting a corresponding compound of Formula I in which R^4, R^5 or R^7 comprises $-X^{13}C(O)OH$ with a compound having the formula $R^6X^{14}NHR^8$, wherein X^{13} and X^{14} are linking groups containing n13 and n14 contiguous linking atoms, respectively, wherein the sum of n13 and n14 is 0 to 10, R^8 is hydrogen or (C_{1-6})alkyl and R^6 is as defined in the Summary of the Invention. The reaction typically is carried out in the presence of 1-hydroxybenzotriazole (HOBT) and a coupling agent (e.g., benzotriazol-1-yloxytrispyrrolidinophosphonium hexafluorophosphate (PyBOP),

1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI), 1,1-carbonyldiimidazole, etc.) and a non-nucleophillic base (e.g., *N*-methylmorpholine, *N,N*-diisopropylethylamine, etc.) and in a suitable solvent (e.g., *N,N*-dimethylformamide (DMF), tetrahydrofuran (THF), dichloromethane, etc., preferably DMF) at 20 to 25 °C and requires 12 to 24 hours to complete (e.g., see Example 3, infra.).

Compounds of Formula I in which R^4, R^5 or R^7 comprises $-X^{13}NR^8C(O)X^{14}R^6$ can be prepared by reacting a corresponding compound of Formula I in which R^4, R^5 or R^7 comprises $-X^{13}NHR^8$ with a compound having the formula $R^6X^{14}C(O)OH$, wherein X^{13} and X^{14} are linking groups containing n13 and n14 contiguous linking atoms, respectively, wherein the sum of n13 and n14 is 0 to 10, R^8 is hydrogen or (C_{1-6})alkyl and R^6 is as defined in the Summary of the Invention. The reaction typically is carried out in the presence of a coupling agent (e.g., PyBOP, EDCI, 1,1-carbonyldiimidazole, etc.) and a non-nucleophillic base (e.g., *N*-methylmorpholine, *N,N*-diisopropylethylamine, etc.) and in a suitable solvent (e.g., DMF, THF, dichloromethane, etc., preferably DMF) at 20 to 25 °C and requires 6 to 24 hours to complete.

Compounds of Formula I in which R^4, R^5 or R^7 comprises $-X^{13}NR^8S(O)_2X^{14}R^6$ can be prepared by reacting a corresponding compound of Formula I in which R^4, R^5 or R^7 comprises $-X^{13}NHR^8$ with a compound having the formula $R^6X^{14}S(O)_2Cl$, wherein X^{13} and X^{14} are linking groups containing n13 and n14 contiguous linking atoms, respectively, wherein the sum of n13 and n14 is 0 to 10, R^8 is hydrogen or (C_{1-6})alkyl and R^6 is as defined in the Summary of the Invention. The reaction typically is carried out in the presence of a non-nucleophillic base (e.g., *N*-methylmorpholine, *N,N*-diisopropylethylamine, etc.) and in a suitable solvent (e.g., DMF, THF, dichloromethane, etc., preferably DMF) at 20 to 25 °C and requires 12 to 24 hours to complete.

Compounds of Formula I in which R^4, R^5 or R^7 comprises $-X^{13}NR^8CH_2X^{14}R^6$ can be prepared by reacting a corresponding compound of Formula I in which R^4, R^5 or R^7 comprises $-X^{13}NHR^8$ with a compound having the formula $R^6X^{14}C(O)H$ under reducing conditions, wherein X^{13} and X^{14} are linking groups containing n13 and n14 contiguous linking atoms, respectively, wherein the sum of n7 and n8 is 0 to 10, R^8 is hydrogen or (C_{1-6})alkyl and R^6 is as defined in the Summary of the Invention. The reaction typically is carried out in the presence of a reducing agent (e.g., sodium cyanoborohydride) and in a

suitable solvent (e.g., methanol) at 20 to 25 °C and requires 12 to 24 hours to complete.

Compounds of Formula I may be prepared as pharmaceutically acceptable acid addition salts by reacting the free base forms of a compound of Formula I with a pharmaceutically acceptable inorganic or organic acid. Alternatively, the pharmaceutically acceptable base addition salts of compounds of Formula I may be prepared by reacting the free acid forms of compounds of Formula I with pharmaceutically acceptable inorganic or organic bases. Inorganic and organic acids and bases suitable for the preparation of the pharmaceutically acceptable salts of compounds of Formula I are set forth in the definitions section of this application. Alternatively, the salt forms of the compounds of Formula I may be prepared using salts of the starting materials or intermediates.

The free acid or free base forms of the compounds of Formula I can be prepared from the corresponding base addition salt or acid addition salt form. For example, compounds of Formula I in an acid addition salt form may be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, etc.). Compounds of Formula I in a base addition salt form may be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc).

The *N*-oxides of compounds of Formula I can be prepared by methods known to those of ordinary skill in the art. For example, *N*-oxides can be prepared by treating an unoxidized form of the compound of Formula I with an oxidizing agent (e.g., trifluoroperacetic acid, permaleic acid, perbenzoic acid, peracetic acid, *meta*-chloroperoxybenzoic acid, etc.) in a suitable inert organic solvent (e.g., a halogenated such as methylene chloride) at approximately 0 °C. Alternatively, the *N*-oxides of the compounds of Formula I can be prepared from the *N*-oxide of an appropriate starting material.

Compounds of Formula I in unoxidized form can be prepared from *N*-oxides of compounds of Formula I by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, etc.) in an suitable inert organic solvent (e.g., acetonitrile, ethanol, aqueous dioxane, etc.) at 0 to 80 °C.

Prodrug derivatives of the compounds of Formula I can be prepared by methods

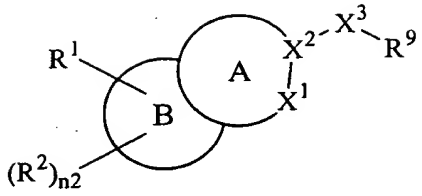
known to those of ordinary skill in the art (e.g., for further details see Saulnier *et al.*(1994), *Bioorganic and Medicinal Chemistry Letters*. 4:1985). For example, appropriate prodrugs can be prepared by reacting a non-derivatized compound of Formula I with a suitable carbamylating agent (e.g., 1,1-acyloxyalkylcarbonochloridate, *para*-nitrophenyl carbonate, etc.).

Protected derivatives of the compounds of Formula I can be made by means known to those of ordinary skill in the art. A detailed description of the techniques applicable to the creation of protective groups and their removal can be found in T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1981.

Compounds of Formula I can be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereomeric compounds, separating the diastereomers and recovering the optically pure enantiomer. While resolution of enantiomers can be carried out using covalent diastereomeric derivatives of compounds of Formula I, dissociable complexes are preferred (e.g., crystalline diastereoisomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromotography or, preferably, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixtures can be found in Jean Jacques, Andre Collet, Samuel H. Wilen, Enantiomers, Racemates and Resolutions, John Wiley & Sons, Inc. (1981).

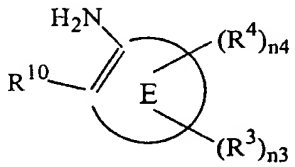
In summary, an aspect of this Invention is a process for preparing a compound of Formula I, which process comprises:

(a) reacting a compound of Formula 1:

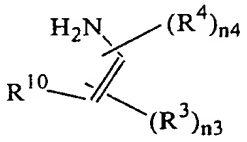


1

or a protected derivative thereof, with a diamine of Formula 2(a) or 2(b):



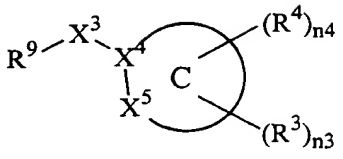
2(a)



2(b)

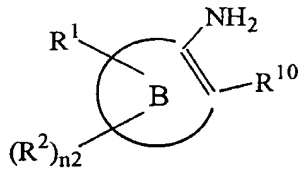
or a protected derivative thereof, in which R^9 is –C(O)L or –CN, wherein L is a leaving group, E together with the vinylene moiety to which it is fused comprises a monocyclic or fused bicyclic divalent radical containing from 5 to 15 annular atoms, wherein each ring contains 5 to 7 annular atoms and optionally one or more annular members is a heteroatom, , X^5 is $N(R^5)$, O or S, R^{10} is –OH, $-NHR^5$ or –SH and heteroatom n2, n3, n4, B, X^1, X^2, X^3, R^1, R^2, R^3, R^5 and R^4 are as defined in the Summary of the Invention, to give a compound of Formula I in which X^4 and X^5 are adjacent members of an oxazol-2-yl, 1*H*-imidazol-2-yl or thiazol-2-yl ring; or

(b) reacting a compound of Formula 3:



3

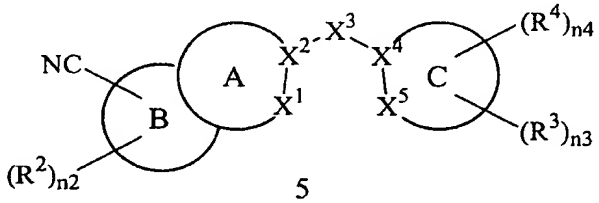
or a protected derivative thereof, with a compound of Formula 4:



4

or a protected derivative thereof, which R^9 is –C(O)L or –CN, wherein L is a leaving group, R^{10} is –OH, $-NHR^5$ or –SH and n2, n3, n3, B, C, X^3, X^4, X^5, R^1, R^2, R^3, R^4 and R^5 are as defined in the Summary of the Invention, to give a compound of Formula I in which X^1 and X^2 are adjacent members of an oxazol-2-yl, 1*H*-imidazol-2-yl or thiazol-2-yl ring; or

(c) reacting a compound of Formula 5:



5

with hydroxylamine hydrochloride, wherein n2, n3, n3, A, B, C, X^1, X^2, X^3, X^4, X^5, R^1, R^2, R^3 and R^4 are as defined above, to give a corresponding *N*-hydroxycarboxamidine and then dehydroxylating;

(e) optionally further reacting a compound of Formula I in which R^4, R^5 or R^7 comprises $-X^{13}C(O)OH$ with a compound having the formula $R^6X^{14}NHR^8$ to give a compound of Formula I in which R^4, R^5 or R^7 comprises $-X^{13}C(O)NR^8X^{14}R^6$, wherein X^{13} and X^{14} are

linking groups containing n13 and n14 contiguous linking atoms, respectively, wherein the sum of n13 and n14 is 0 to 10, R^8 is hydrogen or (C_{1-6})alkyl and R^6 is as defined in the Summary of the Invention;

(f) optionally further reacting a compound of Formula I in which R^4, R^5 or R^7 comprises $-X^{13}NHR^8$ with a compound having the formula $R^6X^{14}C(O)OH$ to give a compound of Formula I in which R^4, R^5 or R^7 comprises $-X^{13}NR^8C(O)X^{14}R^6$, wherein X^{13} and X^{14} are linking groups containing n13 and n14 contiguous linking atoms, respectively, wherein the sum of n13 and n14 is 0 to 10, R^8 is hydrogen or (C_{1-6})alkyl and R^6 is as defined in the Summary of the Invention;

(g) optionally further reacting a compound of Formula I in which R^4, R^5 or R^7 comprises $-X^{13}NHR^8$ with a compound having the formula $R^6X^{14}S(O)_2Cl$ to give a compound of Formula I in which R^4, R^5 or R^7 comprises $-X^{13}NR^8S(O)_2X^{14}R^6$, wherein X^{13} and X^{14} are linking groups containing n13 and n14 contiguous linking atoms, respectively, wherein the sum of n13 and n14 is 0 to 10, R^8 is hydrogen or (C_{1-6})alkyl and R^6 is as defined in the Summary of the Invention;

(h) optionally further reacting a compound of Formula I in which R^4, R^5 or R^7 comprises $-X^{13}NHR^8$ with a compound having the formula $R^6X^{14}C(O)H$ under reducing conditions to give a compound of Formula I in which R^4, R^5 or R^7 comprises $-X^{13}NR^8CH_2X^{14}R^6$, wherein X^{13} and X^{14} are linking groups containing n13 and n14 contiguous linking atoms, respectively, wherein the sum of n13 and n14 is 0 to 10, R^8 is hydrogen or (C_{1-6})alkyl and R^6 is as defined in the Summary of the Invention;

(i) optionally converting a non-salt form of a compound of Formula I to a pharmaceutically acceptable salt with a pharmaceutically acceptable inorganic or organic acid or base;

(j) optionally converting an acid addition salt or base addition salt form of a compound of Formula I to the corresponding free base or free acid, respectively, with a suitable base or acid;

(k) optionally separating a mixture of stereoisomers of a compound of Formula I to give a single stereoisomer;

(l) optionally converting an unoxidized form of a compound of Formula I into a pharmaceutically acceptable *N*-oxide;

(m) optionally converting an *N*-oxide form of a compound of Formula I its unoxidized form;

(n) optionally converting a non-derivatized compound of Formula I into a pharmaceutically prodrug derivative; and

(o) optionally converting a prodrug derivative of a compound of Formula I to its non-derivatized form.

In any of the above processes, a reference to Formula I refers to such Formula wherein each X, R^1, R^2, R^3, R^4 and R^5 are as defined in their broadest definitions set forth in the Summary of the Invention, with the processes applying particularly well to the presently preferred embodiments.

Examples:

EXAMPLE 1

3-(5-Amidino-1*H*-benzimidazol-2-yl)propionic acid,

a compound of Formula 1 in which L is hydroxy, A together with B comprises 5-amidino-1*H*-benzimidazol-2-yl and X^3 is $-CH_2CH_2-$

A mixture comprising succinic anhydride (2.0 g, 19.98 mmol, 1.2 eq.), 3,4-diaminobenzamidine hydrochloride (3.1 g, 16.65 mmol., 1 eq.) and acetic acid (50 mL) was heated at 80 °C for 6 hours to give a precipitate. The precipitate was filtered, washed with excess ethyl acetate and diethyl ether and dried under vacuum to give 3-(5-amidino-1*H*-benzimidazol-2-yl)propionic acid (2.8 g, 11.86 mmol) as an off-white solid.

EXAMPLE 2

Methyl 3-(8-benzyloxyquinolin-2-yl)propionate,

a compound of Formula 3 in which L is methoxy, C comprises 3-(8-benzyloxyquinolin-2-yl) and X^3 is $-CH_2CH_2-$

(a) A mixture comprising 2-methylquinolin-8-ol (8.9 g, 50 mmol), potassium carbonate

(18.8 g, 100 mmol), DMF (85 mL) and benzyl bromide (8.9 mL, 75 mmol) was heated at 60 °C for approximately 12 hours, filtered and concentrated. The residue was dissolved in ethyl acetate and the solution was extracted into 1 N hydrochloric acid. The aqueous layer was made basic with sodium bicarbonate and the product was extracted into ether. The ether solution was dried ($MgSO_4$) and concentrated to provide 8-benzyloxy-2-methylquinoline (10 g, 80 %) as a white solid.

(b) A solution comprising selenium dioxide (3.3 g, 30 mmol) in dioxane (60 mL) and water (1.5 mL) was warmed in a water bath and then 8-benzyloxy-2-methylquinoline (5.0 g, 20 mmol) was added portion-wise to the solution over 15 minutes. The mixture was heated at 50° C for 7 hours, cooled in an ice bath, filtered and concentrated to give orange crystals. The crystals were dissolved in hot hexanes, leaving a red residue behind. The solution was cooled to provide yellow crystals. The crystals were isolated and dried to provide 8-benzyloxyquinoline-2-carbaldehyde (3.9 g, 74%).

(c) A solution comprising potassium hydride (448 mg, 11.2 mmol), THF (10 mL), and trimethylphosphonoacetate (1.81 mL, 11.2 mmol) was stirred for 45 minutes, then added over 15 minutes to a solution comprising 8-benzyloxyquinoline-2-carboxaldehyde (1.34 g, 5.6 mmol) in THF (10 mL). The mixture was quenched with ammonium chloride after 2 hours and then extracted with methylene chloride. The extract was washed with 0.5 N sodium hydroxide, dried ($MgSO_4$), and concentrated to provide methyl 3-(8-benzyloxyquinolin-2-yl)acrylate (1.5 g, 94%) as a yellow solid.

(d) A mixture comprising methyl 3-(8-benzyloxyquinolin-2-yl)acrylate (1.5 g, 4.7 mmol), methanol (50 mL) and a catalytic amount of 10% palladium on carbon was stirred under hydrogen balloon at room temperature for 15 hours, filtered through Celite and concentrated. The residue was purified by chromatography on silica (25% ethyl acetate in hexanes) to provide methyl 3-(8-benzyloxyquinolin-2-yl)propionate (550 mg, 51%).

EXAMPLE 3

2-[2-(1*H*-Benzimidazol-2-yl)ethyl]-1*H*-benzimidazole-5-carboxamidine (Compound 1),

a compound of Formula I in which A together with B comprises 5-amidino-1*H*-benzimidazol-2-yl, C comprises 1*H*-benzimidazol-2-yl and X^3 is $-CH_2CH_2-$

A mixture comprising 3-(5-amidino-1*H*-benzimidazol-2-yl)propionic acid (1 g, 5.26 mmol), 1,2-benzenediamine dihydrochloride (0.98 g, 5.26 mmol) and polyphosphoric acid (3 mL) was heated at 180° C for 3 hours. The mixture was cooled, diluted with water (2 mL) and basified with 10N sodium hydroxide to pH 8 to give a precipitate. The precipitate was collected and washed with water. The residue was purified by reverse phase HPLC (1% trifluoroacetic acid/acetonitrile) with a 2-27% gradient. The resulting pure fractions were lyophilized to provide 2-[2-(1*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazole-5-carboxamidine (1.4 g, 3.34 mmol) as a white solid, MS (ESI): Calculated for $C_{17}H_{16}N_6$: MH^+: 304.35 Found: MH^+ 304.9.

Proceeding as in Example 3, but substituting different starting materials, provided the following Formula I:

2-[2-(1-methyl-1*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazole-5-carboxamidine (Compound 2), Calculated for $C_{18}H_{18}N_6$: MH^+: 318.16 Found: MH^+ 318.8;

2-[2-(1-benzyl-1*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazole-5-carboxamidine (Compound 3), Calculated for $C_{24}H_{22}N_6$: MH^+: 394.19 Found: MH^+ 394.6;

2-[2-(1-pyrid-4-yl-1*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazole-5-carboxamidine (Compound 4), Calculated for $C_{22}H_{19}N_7$: MH^+: 381.2 Found: MH^+ 381.9;

2-[2-(1*H*-imidazo[4,5-*c*]pyrid-2-yl)ethyl]-1*H*-benzimidazole-5-carboxamidine (Compound 5); Calculated for $C_{16}H_{15}N_7$: MH^+: 305.14 Found: MH^+ 306.1;

2-[2-(9*H*-purin-8-yl)ethyl]-1*H*-benzimidazole-5-carboxamidine (Compound 6); Calculated

for $C_{16}H_{15}N_7$: MH^+: 306.13 Found: MH^+ 307.2;

2-[2-(5-imidazol-1-yl-1-*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazole-5-carboxamidine (Compound 7); Calculated for $C_{20}H_{18}N_8$: MH^+: 370.17 Found: MH^+ 370.9;

2-[2-(1*H*-naptho[2,3-*d*]imidazol-2-yl)ethyl]-1*H*-benzimidazole-5-carboxamidine (Compound 8); Calculated for $C_{18}H_{18}N_6$: MH^+: 354.16 Found: MH^+ 355.0;

2-[2-(5-benzoyl-1-*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazole-5-carboxamidine (Compound 9); Calculated for $C_{24}H_{20}N_6O$: MH^+: 408.17 Found: MH^+ 409.0;

2-[2-(5-chloro-1*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazole-5-carboxamidine (Compound 10); Calculated for $C_{17}H_{15}ClN_6$: MH^+: 338.1 Found: MH^+ 338.8;

2-[2-(5-fluoro-1-*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazole-5-carboxamidine (Compound 11); Calculated for $C_{17}H_{15}N_5F$: MH^+: 322.13 Found: MH^+ 322.9;

2-[2-(5-(4-aminophenoxy)-1-*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazole-5-carboxamidine (Compound 12); Calculated for $C_{23}H_{21}N_7O$: MH^+: 411.18 Found: MH^+ 412;

2-[2-(5,6-difluoro-1-*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazole-5-carboxamidine (Compound 13); Calculated for $C_{17}H_{14}N_6F_2$: MH^+: 340.12 Found: MH^+ 341.0;

methyl 2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazole-5-carboxylate (Compound 14); Calculated for $C_{19}H_{18}N_6O_2$: MH^+: 362.39 Found: MH^+ 363.2;

2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazole-5-carboxylic acid (Compound 15); Calculated for $C_{18}H_{16}N_6O_2$: MH^+: 348.36 Found: MH^+ 348.9;

methyl 2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-3-methyl-3*H*-benzimidazole-5-carboxylate (Compound 16); Calculated for $C_{20}H_{20}N_6O_2$: MH^+: 376.42 Found: MH^+ 377.1;

2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-3-methyl-3*H*-benzimidazole-5-carboxylic acid (Compound 17); Calculated for $C_{19}H_{18}N_6O_2$: MH^+: 362.39 Found: MH^+ 363;

2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-1-methyl-1*H*-benzimidazole-5-carboxylic acid (Compound 18); Calculated for $C_{19}H_{18}N_6O_2$: MH^+: 362.39 Found: MH^+ 363;

2-[2-(1*H*-benzimidazol-2-yl)ethyl]-3-(3-phenylpropyl)-3*H*-benzimidazole-5-carboxamidine (Compound 19); Calculated for $C_{26}H_{26}N_6$: MH^+: 422.53 Found: MH^+ 423;

trans-2-[2-(1*H*-benzimidazol-2-yl)-1-methylpropenyl]-3*H*-benzimidazole-5-carboxamidine (Compound 20); Calculated for $C_{19}H_{18}N_6$: MH^+: 330.16 Found: MH^+ 331.0;

2-[2-(1*H*-benzimidazol-2-yl)cyclohex-1-enyl]-3*H*-benzimidazole-5-carboxamidine (Compound 21); Calculated for $C_{21}H_{20}N_6$: MH^+: 356.17 Found: MH^+ 357;

2-[2-(1*H*-benzimidazol-2-yl)phenyl]-3*H*-benzimidazole-5-carboxamidine (Compound 22); Calculated for $C_{21}H_{16}N_6$: MH^+: 352.14 Found: MH^+ 352.9;

2-[2-(1*H*-imidazo[4,5-*c*]pyrid-2-yl)phenyl]-3*H*-benzimidazole-5-carboxamidine (Compound 23); Calculated for $C_{20}H_{15}N_7$: MH^+: 353.14 Found: MH^+ 353.9; and

2-(2-benzothiazol-2-ylethyl)-1*H*-benzimidazole-5-carboxamidine (Compound 24); Calculated for $C_{17}H_{15}N_5S$: MH^+: 321.1 Found: MH^+ 321.9.

EXAMPLE 4

2-[2-(8-Hydroxyquinolin-2-yl)ethyl]-1*H*-benzimidazole-5-carboxamidine (Compound 35),

a compound of Formula I in which A together with B comprises 5-amidino-1*H*-benzimidazol-2-yl, C comprises 8-hydroxyquinolin-2-yl and X^3 is $-CH_2CH_2-$

A mixture comprising methyl 3-(8-benzyloxyquinolin-2-yl)acrylate (550 mg, 2.4 mmol), DMPU (2 mL) and diaminobenzamidine hydrochloride (448 mg, 2.4 mmol) in a sealed pressure tube was heated at 180 °C for 3 hours, allowed to cool to 100 °C, and diluted with acetonitrile to give a yellow precipitate (790 mg, 99%). The product was further purified by reverse phase HPLC using a two solvent system (solvent A: 20 mM HCl in H_2O; solvent B: CH_3CN) with programmed elution at 50 mL/min (0 min, 98% A, 2% B; 15 min, 98% A, 2% B; 50 min, 73% A, 27% B) on a C18 preparatory column. ^1H NMR δ 10.6 (bs, 1 H), 9.5 (s, 2 H), 9.1 (s, 2H), 8.5 (d, 1 H, J = 10 Hz), 8.2 (s, 1 H), 7.9 (d, 1 H, J =

10 Hz), 7.8 (d, 1 H, J = 10 Hz), 7.7 (d, 1 H, J = 10 Hz), 7.5 (s, 2 H), 7.2 (s, 1 H), 3.7 (s, 4 H). LRMS (Bioion) calcd $C_{19}H_{17}N_5O$ + H 332.1; found 332.2.

EXAMPLE 5

3-(5-Amidino-1*H*-benzimidazol-2-yl)-2-(1*H*-benzimidazol-2-yl)propionamide

(Compound 31),

a compound of Formula I in which A together with B comprises 5-amidino-1*H*-benzimidazol-2-yl, C comprises 1*H*-benzimidazol-2-yl and X^3 is carbamoylethylene

A mixture of ethyl 2-(1*H*-benzimidazol-2-yl)-3-cyanopropionate (0.5 g, 2.06 mmol) and 3,4-diaminobenzamidine hydrochloride (0.32 g, 1.71 mmol) was heated at 180 °C for 2 hours and concentrated. The residue was taken up in 0.1 N hydrochloric acid and purified by reverse HPLC (1% TFA/acetonitrile) with a 2-27% gradient to provide 3-(5-amidino-1*H*-benzimidazol-2-yl)-2-(1*H*-benzimidazol-2-yl)propionamide (0.15 g) as a white solid, Electrospray MS (ESI): Calculated for $C_{18}H_{16}N_6O_1$: MH^+: 332.36 Found: MH^+ 333.

EXAMPLE 6

Methyl 3-(5-amidino-1*H*-benzimidazol-2-yl)-2-(1*H*-benzimidazol-2-yl)propionate (Compound 32),

a compound of Formula I in which A together with B comprises 5-amidino-1*H*-benzimidazol-2-yl, C comprises 1*H*-benzimidazol-2-yl and X^3 is methoxycarbonyl

A solution comprising 3-(5-amidino-1*H*-benzimidazol-2-yl)-2-(1*H*-benzimidazol-2-yl)propionamide (50 mg) hydrogen chloride/dioxane (4M, 5 mL) and methanol (10mL) in a sealed tube was heated overnight and concentrated. The residue was purified by reverse HPLC (1% TFA/acetonitrile) with a 2-27% gradient to provide methyl 3-(5-amidino-1*H*-benzimidazol-2-yl)-2-(1*H*-benzimidazol-2-yl)propionate (0.01 g) as an off-white solid, Calculated for $C_{19}H_{18}N_6O_2$: MH^+: 326.39 Found: MH^+ 362.9.

EXAMPLE 7

2-[2-(5-Amidino-1*H*-benzimidazol-2-yl)ethyl]-*N*-benzyl-3*H*-benzimidazole-5-carboxamide (Compound 25),

a compound of Formula I in which A together with B comprises 5-amidino-1*H*-benzimidazol-2-yl, C comprises 5-benzylcarbamoyl-1*H*-benzimidazol-2-yl and X^3 is $-CH_2CH_2-$

A mixture comprising 2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole-5-carboxylic acid (0.4 g, 1.15 mmol), EDC (0.265 g, 1.38 mmol), HOBT (0.187 g, 1.38 mmol), NMM (0.35 g, 3.45 mmol, 0.38 mL) and THF (20 mL) was stirred at room temperature 1 hour and then benzylamine (0.25 g, 2.3 mmol) was added. The mixture was over night, poured into ether and decanted. The residue was taken up in 0.01 N hydrochoric acid and purified by reverse HPLC (1% TFA/acetonitrile) with a 2-27% gradient to provide 2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-*N*-benzyl-3*H*-benzimidazole-5-carboxamide (0.18 g) as a bright yellow solid, MS (ESI): Calculated

for $C_{25}H_{23}N_7O$: MH^+: 437.5 Found: MH^+ 438.

Proceeding as in Example 7, but substituting different starting materials, provided the following compounds of Formula I:

2-{2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazol-5-ylcarbonylamino}propionic acid (Compound 26); Calculated for $C_{21}H_{21}N_7O_3$: MH^+: 419.44 Found: MH^+ 420;

2-{2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazol-5-ylcarbonylamino}pentandioic acid (Compound 27); Calculated for $C_{23}H_{23}N_7O_5$: MH^+: 477.48 Found: MH^+ 478.4;

2-{2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazol-5-ylcarbonylamino}-3-phenylpropionic acid (Compound 28); Calculated for $C_{27}H_{25}N_7O_3$: MH^+: 496.5 Found: MH^+ 495.54;

2-{2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazol-5-ylcarbonylamino}-3-methylbutyric acid (Compound 29); Calculated for $C_{23}H_{25}N_8O_3$: MH^+: 447.5 Found: MH^+ 448.4; and

6-amino-2-{2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazol-5-ylcarbonylamino}-3-methylhexanoic acid (Compound 30).

EXAMPLE 8

In Vitro Enzyme Inhibitor Assay

The following represents an assay for determining the Factor Xa inhibitory activity of compounds of Formula I.

Mixtures of human Factor Xa (0.5-5 nM) and test compound (varying concentrations) in assay medium (comprising: Tris, 50 mM (pH 8); NaCl, 1M; $CaCl_2$, 5 mM; polyoxyethylenesorbitan monolaurate (Tween-20), 0.05%; DMSO, 10%; and zinc chloride, 150 μM) were incubated for 1 hour at room temperature and then substrate, MesOC-Norleu-Gly-Arg-pNA, was added such that the final concentration of the assay mixture was between 0.5 and 5 mM. Hydrolysis of the substrate was followed spectrophotometrically at (405 λ) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

Proceeding as described in this application or by methods known to those of ordinary skill the following compounds of Formula I were prepared and tested for factor Xa inhibitory activity:

Compound 3, K_i=0.002μM; Compound 7, K_i=0.0009μM; Compound 9, K_i=0.0008μM; Compound 12, K_i=0.0007μM; Compound 15, K_i=0.006μM; Compound 16, K_i=0.00002μM; Compound 17, K_i=0.001μM; Compound 19, K_i=0.003μM; Compound 20, K_i=0.003μM; Compound 21, K_i=0.004μM; Compound 22, K_i=0.003μM; Compound 25, K_i=0.0005μM; Compound 26, K_i=0.003μM; Compound 27, K_i=0.004μM; Compound 28, K_i=0.006μM; Compound 29, K_i=0.003μM; Compound 30, K_i=0.005μM; and Compound 31, K_i=0.002μM.

EXAMPLE 9

Ex vivo ACT Assay

Rabbits were sedated with Hypnorm® (fluanisone 10 mg/mL and phentanylcitrate 0.315 mg/mL; 0.05 mL/kg, i.m.). A catheter (Venflon®2, ⌀ 0.8/25 mm) was inserted into a marginal ear vein for adminstration of test compound. A second catheter (Venflon®2, ⌀ 1.0/32 mm) was inserted into the artery of the other ear for blood sampling. Test compounds were administered by i.v. bolus injection. Blood samples were collected (0.5 mL) prior to adminstration of test compounds and at various time points thereafter.

The activating clotting time (ACT), the amount of time for clot formation, was measured with a Medtronic Automated Coagulation Timer ACT II. An aliquot (200 µL) of the blood sample was added to each of two reaction chambers of a disposable two-channel test cartridge containing assay buffer (comprising: 0.75% kaolin, as the activator, and 0.0025M $CaCl_2$ in 0.1 mL HEPES buffer for non-citrated blood and 2.2% kaolin and 0.05M $CaCl_2$ in 0.1 mL HEPES buffer for citrated blood). Clot formation was measured as a decrease in the downward motion of a plunger assembly contained by the test cartridge. The decrease in downward motion of the plunger was detected by a photo-optic system.

Proceeding as described in Example 9 compounds of the present Invention were assayed and found to increase ACT.

EXAMPLE 10

In vitro ACT Assay

Rabbit blood was collected from an indwelling catheter in a ear artery into plastic containers. Human blood was collected via venipuncture into vacutainers, some of which contained 0.5 mL of 3.8% citrate. ACT was measured as described in Example 7. Blood samples were mixed with varying concentrations of test compounds dissolved in physiological saline (30μL for non-citrated blood and 15μL for citrated blood). Non-citrated blood was used in the assay immediately upon its collection. Citrated blood was kept at ambient temperature for 0.5 to 2 hours and then incubated at 37 °C before used.

Proceeding as described in Example 10compounds of the present Invention were assayed and found to increased ACT.

EXAMPLE 11

The following are representative pharmaceutical formulations containing a compound of Formula I.

ORAL FORMULATION

	10-100 mg
Compound of Formula I	105 mg
Citric Acid Monohydrate	18 mg
Sodium Hydroxide	
Flavoring	q.s. to 100 mL
Water	

INTRAVENOUS FORMULATION

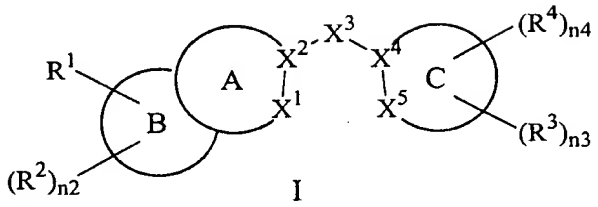
Compound of Formula I	0.1-10 mg
Dextrose Monohydrate	q.s. to make isotonic
Citric Acid Monohydrate	1.05 mg
Sodium Hydroxide	0.18 mg
Water for Injection	q.s. to 1.0 mL

TABLET FORMULATION

Compound of Formula I	1%
Microcrystalline Cellulose	73%
Stearic Acid	25%
Colloidal Silica	1%.

WE CLAIM:

1. A compound of Formula I:



I

in which:

n2 is 1, 2 or 3;

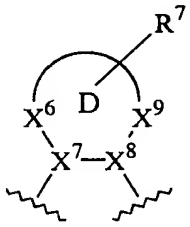
n3 is 1, 2, 3 or 4;

n4 is 1 or 2;

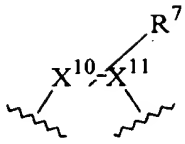
A together with B comprises a fused heterobicyclic radical containing 8 to 12 annular atoms, wherein each ring contains 5 to 7 annular members, each annular atom optionally is a heteroatom, X^1 and X^2 are adjacent annular members of an aromatic ring and X^1 is a heteroatom moiety selected from -N=, $-NR^5-$, -O- and -S-, wherein R^5 is $-R^6$ or $-X^6-R^6$, wherein X^6 is a linking group containing 1 to 12 contiguous linking atoms and R^6 is hydrogen, (C_{6-14})aryl, cyclo(C_{3-14})alkyl, hetero(C_{5-14})aryl, heterocyclo(C_{3-14})alkyl, hetero(C_{8-14})polycycloaryl or (C_{9-14})polycycloaryl;

C comprises a heteromonocyclic or fused heteropolycyclic radical containing 5 to 18 annular atoms, wherein each ring contains 5 to 7 annular members, each annular atom optionally is a heteroatom, X^4 and X^5 are adjacent annular members of an aromatic ring and X^5 is a heteroatom moiety selected from -N=, $-NR^5-$, -O- and -S-, wherein R^5 is as defined above, and any carbocyclic ketone, thioketone and iminoketone derivative thereof;

X^3 represents a linking group of Formula (a) or (b):



(a)



(b)

in which D comprises a monocyclic or polycyclic divalent radical containing 5 to 10 annular atoms, wherein X^6, X^7, X^8 and X^9 are contiguous annular carbon atoms and one or more other annular atoms optionally is a heteroatom moiety heteroatom moiety selected from –N=, $-NR^5-$, –O– and –S–, wherein R^5 is as defined above, X^{10} and X^{11} together represent a linking group containing two contiguous linking atoms and R^7 is $-R^6$ or $-X^6-R^6$, wherein X^6 and R^6 are as defined above, with the proviso that when X^3 is a linking group of Formula (b) and R^7 is $-R^6$, wherein R^6 is substituted or unsubstituted heteroaryl or heteropolycycloaryl, then the annular atom of R^6 to which X^{10} or X^{11} is attached is not adjacent to an annular heteroatom moiety;

R^1 is amidino and bonded to any annular carbon atom with an available valence comprising B;

each R^2 is independently hydrogen, (C_{1-3})alkyl, (C_{1-3})alkyloxy, (C_{1-3})alkylsulfonyl, (C_{1-3})alkylthio, carboxy, halo, (C_{2-12})heteroalkyl, hydroxy, mercapto or nitro and bonded to any annular atom with an available valence comprising B;

each R^3 is independently hydrogen, cyano, halo, nitro, perhalo(C_{1-3})alkyl or perhalo(C_{1-3})alkyloxy and bonded to any annular atom with an available valence comprising C; and

each R^4 is independently $-R^6$ or $-X^6-R^6$, wherein X^6 and R^6 are as defined above, and bonded to any annular atom with an available valence comprising C;

wherein aliphatic or alicyclic moieties with an available valence comprising each X^6 and R^6 optionally are substituted with 1 to 5 substituents independently selected from (C_{1-6})alkyl, (C_{1-6})alkylamino, di(C_{1-6})alkylamino, (C_{1-6})alkylcarbamoyl, di(C_{1-6})alkylcarbamoyl, (C_{1-6})alkyloxy, (C_{1-6})alkyloxycarbonyl, (C_{1-6})alkylsulfinyl, (C_{1-6})alkylsulfonyl, (C_{1-6})alkylthio, amino, carbamoyl, carboxy, cyano, guanidino, halo, hydroxy, mercapto, perhalo(C_{1-3})alkyl, perhalo(C_{1-3})alkyloxy and uriedo; and aromatic moieties with an available valence comprising each X^6 and R^6 optionally are substituted with one to three substituents independently selected from (C_{1-3})alkyl, (C_{1-3})alkylamino, di(C_{1-3})alkylamino, (C_{1-3})alkyloxy, (C_{1-3})alkyloxycarbonyl, (C_{1-3})alkylimino, amino, carboxy, cyano, guanidino, halo, hydroxy, perhalo(C_{1-3})alkyl and perhalo(C_{1-3})alkyloxy; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

2. The compound of Claim 1 in which:

n2 is 1;

A together with B comprises a fused heterobicyclic radical containing 8 to 10 annular atoms, wherein each ring contains 5 to 6 annular members;

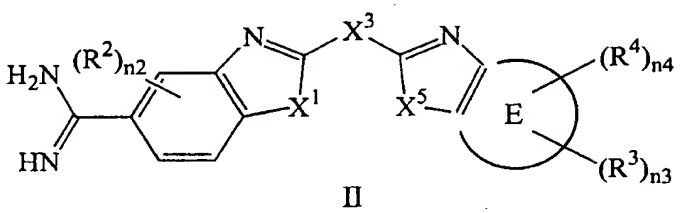
C comprises a fused heteropolycyclic radical containing from 9 to 13 annular atoms, wherein each ring contains 5 to 6 annular atoms;

X^3 represents a linking group of Formula (a) or (b) in which D comprises a monocyclic divalent radical containing 6 annular carbon atoms;

each R^3 is independently hydrogen, halo or hydroxy; and

each R^4, R^5 and R^7 is independently $-R^6$ or $-X^6-R^6$, wherein X^6 is a linking group containing 1 to 10 contiguous linking atoms and R^6 is hydrogen, (C_{6-10})aryl, cyclo(C_{3-6})alkyl, hetero(C_{5-10})aryl, heterocyclo(C_{5-6})alkyl or hetero(C_{8-10})polycycloaryl; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

3. The compound of Claim 2 which is a compound of Formula II:



II

in which E together with the vinylene moiety to which it is fused comprises a monocyclic or heteromonocyclic divalent radical containing 6 annular atoms; X^3 is ethylene, carbamoylethylene, methoxycarbonylethylene, *trans*-1,2-methylvinylene, 1,2-phenylene or 1-cyclohexen-1,2-ylene; and X^1 and X^5 are independently a heteroatom moiety selected from $-NR^5-$, $-O-$ and $-S-$; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

4. The compound of Claim 3 in which each R^4, R^5 and/or R^7 is independently $-R^6$, wherein R^6 is (C_{6-14})aryl, cyclo(C_{3-14})alkyl, hetero(C_{5-14})aryl, heterocyclo(C_{3-14})alkyl, hetero(C_{8-14})polycycloaryl or (C_{9-14})polycycloaryl, or $-X^6-R^6$, wherein X^6 is (C_{1-10})alkylene, or (C_{2-10})heteroalkylene and R^6 is hydrogen, (C_{6-14})aryl, cyclo(C_{3-14})alkyl, hetero(C_{5-14})aryl, heterocyclo(C_{3-14})alkyl, hetero(C_{8-14})polycycloaryl or (C_{9-14})polycycloaryl; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

5. The compound of Claim 3 in which each R^3 is independently cyano, halo, nitro, perhalo(C_{1-3})alkyl or perhalo(C_{1-3})alkyloxy and/or each R^4 is independently hydroxy, mercapto, sulfo, $-NHR^8$ or $-OP(O)(OR^8)OH$, wherein R^8 is hydrogen or (C_{1-6})alkyl; and the *N*-oxide derivatives,

prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

6. The compound of Claim 3 in which one of X^1 and X^5 is $-NR^5-$ and the other is a heteroatom selected from –O– and –S–; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

7. The compound of claim 6 in which X^1 is –S– and X^5 is $-NR^5-$; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

8. The compound of Claim 4 selected from:

methyl 2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-3-methyl-3*H*-benzimidazole-5-carboxylate;

2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-*N*-benzyl-3*H*-benzimidazole-5-carboxamide;

3-(5-amidino-1*H*-benzimidazol-2-yl)-2-(1*H*-benzimidazol-2-yl)propionamide;

2-[2-(5-imidazol-1-yl-1-*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazole-5-carboxamidine;

2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-3-methyl-3*H*-benzimidazole-5-carboxylic acid;

2-[2-(1-benzyl-1*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazole-5-carboxamidine;

2-[2-(1*H*-benzimidazol-2-yl)ethyl]-3-(3-phenylpropyl)-3*H*-benzimidazole-5-carboxamidine;

2-{2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazol-5-ylcarbonylamino}-3-methylbutyric acid;

2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazole-5-carboxylic acid;

2-{2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazol-5-ylcarbonylamino}pentandioic acid;

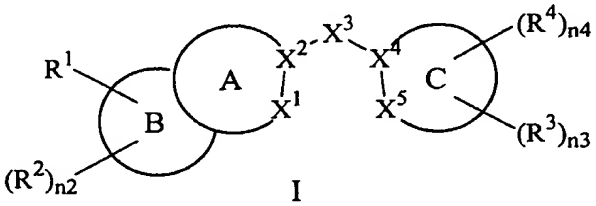
6-amino-2-{2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazol-5-ylcarbonylamino}-3-methylhexanoic acid;

2-{2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazol-5-ylcarbonylamino}propionic acid; and

2-{2-[2-(5-amidino-1*H*-benzimidazol-2-yl)ethyl]-1*H*-benzimidazol-5-ylcarbonylamino}-3-phenylpropionic acid; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

9. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 or a *N*-oxide derivative, prodrug derivative, individual isomer, mixture of isomers or pharmaceutically acceptable salt thereof in admixture with one or more suitable excipients.

10. A method of treating a disease in an animal in which anticoagulation can prevent, inhibit or ameliorate the pathology and/or symptomatology of the disease, which method comprises administering to the animal a therapeutically effective amount of compound of Formula I:



I

in which:

n2 is 1, 2 or 3;

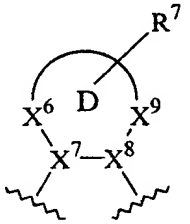
n3 is 1, 2, 3 or 4;

n4 is 1 or 2;

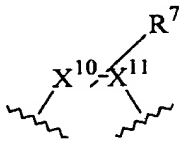
A together with B comprises a fused heterobicyclic radical containing 8 to 12 annular atoms, wherein each ring contains 5 to 7 annular members, each annular atom optionally is a heteroatom, X^1 and X^2 are adjacent annular members of an aromatic ring and X^1 is a heteroatom moiety selected from –N=, –NR^5–, –O– and –S–, wherein R^5 is –R^6 or –X^6–R^6, wherein X^6 is a linking group containing 1 to 12 contiguous linking atoms and R^6 is hydrogen, (C_{6-14})aryl, cyclo(C_{3-14})alkyl, hetero(C_{5-14})aryl, heterocyclo(C_{3-14})alkyl, hetero(C_{8-14})polycycloaryl or (C_{9-14})polycycloaryl;

C comprises a heteromonocyclic or fused heteropolycyclic radical containing 5 to 18 annular atoms, wherein each ring contains 5 to 7 annular members, each annular atom optionally is a heteroatom, X^4 and X^5 are adjacent annular members of an aromatic ring and X^5 is a heteroatom moiety selected from –N=, –NR^5–, –O– and –S–, wherein R^5 is as defined above, and any carbocyclic ketone, thioketone and iminoketone derivative thereof;

X^3 represents a linking group of Formula (a) or (b):



(a)



(b)

in which D comprises a monocyclic or polycyclic divalent radical containing 5 to 10 annular atoms, wherein X^6, X^7, X^8 and X^9 are contiguous annular carbon atoms and one or more other annular atoms optionally is a heteroatom moiety heteroatom moiety selected

from -N=, -NR^5-, -O- and -S-, wherein R^5 is as defined above, X^{10} and X^{11} together represent a linking group containing two contiguous linking atoms and R^7 is -R^6 or -X^6-R^6, wherein X^6 and R^6 are as defined above, with the proviso that when X^3 is a linking group of Formula (b) and R^7 is -R^6, wherein R^6 is substituted or unsubstituted heteroaryl or heteropolycycloaryl, then the annular atom of R^6 to which X^{10} or X^{11} is attached is not adjacent to an annular heteroatom moiety;

R^1 is amidino and bonded to any annular carbon atom with an available valence comprising B;

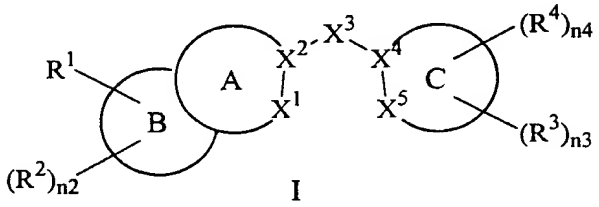
each R^2 is independently hydrogen, (C_{1-3})alkyl, (C_{1-3})alkyloxy, (C_{1-3})alkylsulfonyl, (C_{1-3})alkylthio, carboxy, halo, (C_{2-12})heteroalkyl, hydroxy, mercapto or nitro and bonded to any annular atom with an available valence comprising B;

each R^3 is independently hydrogen, cyano, halo, nitro, perhalo(C_{1-3})alkyl or perhalo(C_{1-3})alkyloxy and bonded to any annular atom with an available valence comprising C; and

each R^4 is independently -R^6 or -X^6-R^6, wherein X^6 and R^6 are as defined above, and bonded to any annular atom with an available valence comprising C;

wherein aliphatic or alicyclic moieties with an available valence comprising each X^6 and R^6 optionally are substituted with 1 to 5 substituents independently selected from (C_{1-6})alkyl, (C_{1-6})alkylamino, di(C_{1-6})alkylamino, (C_{1-6})alkylcarbamoyl, di(C_{1-6})alkylcarbamoyl, (C_{1-6})alkyloxy, (C_{1-6})alkyloxycarbonyl, (C_{1-6})alkylsulfinyl, (C_{1-6})alkylsulfonyl, (C_{1-6})alkylthio, amino, carbamoyl, carboxy, cyano, guanidino, halo, hydroxy, mercapto, perhalo(C_{1-3})alkyl, perhalo(C_{1-3})alkyloxy and uriedo; and aromatic moieties with an available valence comprising each X^6 and R^6 optionally are substituted with one to three substituents independently selected from (C_{1-3})alkyl, (C_{1-3})alkylamino, di(C_{1-3})alkylamino, (C_{1-3})alkyloxy, (C_{1-3})alkyloxycarbonyl, (C_{1-3})alkylimino, amino, carboxy, cyano, guanidino, halo, hydroxy, perhalo(C_{1-3})alkyl and perhalo(C_{1-3})alkyloxy; or a *N*-oxide derivative, prodrug derivative, individual isomer, mixture of isomers or pharmaceutically acceptable salt thereof.

11. A process for preparing a compound of Formula I:



I

in which:

n2 is 1, 2 or 3;

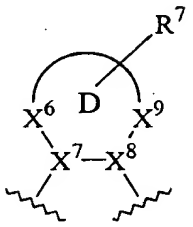
n3 is 1, 2, 3 or 4;

n4 is 1 or 2;

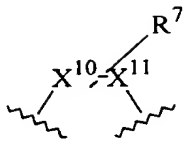
A together with B comprises a fused heterobicyclic radical containing 8 to 12 annular atoms, wherein each ring contains 5 to 7 annular members, each annular atom optionally is a heteroatom, X^1 and X^2 are adjacent annular members of an aromatic ring and X^1 is a heteroatom moiety selected from –N=, –NR^5–, –O– and –S–, wherein R^5 is –R^6 or –X^6–R^6, wherein X^6 is a linking group containing 1 to 12 contiguous linking atoms and R^6 is hydrogen, (C_{6-14})aryl, cyclo(C_{3-14})alkyl, hetero(C_{5-14})aryl, heterocyclo(C_{3-14})alkyl, hetero(C_{8-14})polycycloaryl or (C_{9-14})polycycloaryl;

C comprises a heteromonocyclic or fused heteropolycyclic radical containing 5 to 18 annular atoms, wherein each ring contains 5 to 7 annular members, each annular atom optionally is a heteroatom, X^4 and X^5 are adjacent annular members of an aromatic ring and X^5 is a heteroatom moiety selected from –N=, –NR^5–, –O– and –S–, wherein R^5 is as defined above, and any carbocyclic ketone, thioketone and iminoketone derivative thereof;

X^3 represents a linking group of Formula (a) or (b):



(a)



(b)

in which D comprises a monocyclic or polycyclic divalent radical containing 5 to 10 annular atoms, wherein X^6, X^7, X^8 and X^9 are contiguous annular carbon atoms and one or more other annular atoms optionally is a heteroatom moiety heteroatom moiety selected from –N=, $-NR^5-$, –O– and –S–, wherein R^5 is as defined above, X^{10} and X^{11} together represent a linking group containing two contiguous linking atoms and R^7 is $-R^6$ or $-X^6-R^6$, wherein X^6 and R^6 are as defined above, with the proviso that when X^3 is a linking group of Formula (b) and R^7 is $-R^6$, wherein R^6 is substituted or unsubstituted heteroaryl or heteropolycycloaryl, then the annular atom of R^6 to which X^{10} or X^{11} is attached is not adjacent to an annular heteroatom moiety;

R^1 is amidino and bonded to any annular carbon atom with an available valence comprising B;

each R^2 is independently hydrogen, (C_{1-3})alkyl, (C_{1-3})alkyloxy, (C_{1-3})alkylsulfonyl, (C_{1-3})alkylthio, carboxy, halo, (C_{2-12})heteroalkyl, hydroxy, mercapto or nitro and bonded to any annular atom with an available valence comprising B;

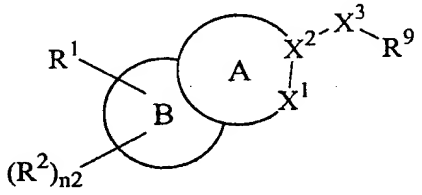
each R^3 is independently hydrogen, cyano, halo, nitro, perhalo(C_{1-3})alkyl or perhalo(C_{1-3})alkyloxy and bonded to any annular atom with an available valence comprising C; and

each R^4 is independently $-R^6$ or $-X^6-R^6$, wherein X^6 and R^6 are as defined above, and bonded to any annular atom with an available valence comprising C;

wherein aliphatic or alicyclic moieties with an available valence comprising each X^6 and R^6 optionally are substituted with 1 to 5 substituents independently selected from

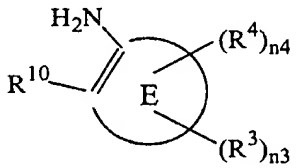
(C_{1-6})alkyl, (C_{1-6})alkylamino, di(C_{1-6})alkylamino, (C_{1-6})alkylcarbamoyl, di(C_{1-6})alkylcarbamoyl, (C_{1-6})alkyloxy, (C_{1-6})alkyloxycarbonyl, (C_{1-6})alkylsulfinyl, (C_{1-6})alkylsulfonyl, (C_{1-6})alkylthio, amino, carbamoyl, carboxy, cyano, guanidino, halo, hydroxy, mercapto, perhalo(C_{1-3})alkyl, perhalo(C_{1-3})alkyloxy and uriedo; and aromatic moieties with an available valence comprising each X^6 and R^6 optionally are substituted with one to three substituents independently selected from (C_{1-3})alkyl, (C_{1-3})alkylamino, di(C_{1-3})alkylamino, (C_{1-3})alkyloxy, (C_{1-3})alkyloxycarbonyl, (C_{1-3})alkylimino, amino, carboxy, cyano, guanidino, halo, hydroxy, perhalo(C_{1-3})alkyl and perhalo(C_{1-3})alkyloxy; and the *N*-oxide derivatives, prodrug derivative, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof; which process comprises:

(a) reacting a compound of Formula 1:

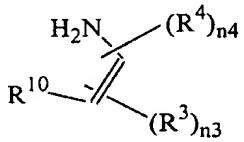


1

or a protected derivative thereof, with a diamine of Formula 2(a) or 2(b):



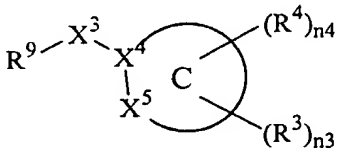
2(a)



2(b)

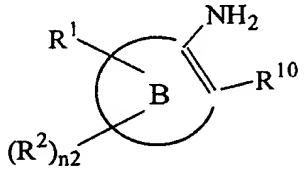
or a protected derivative thereof, in which R^9 is -C(O)L or -CN, wherein L is a leaving group, E together with the vinylene moiety to which it is fused comprises a monocyclic or fused bicyclic divalent radical containing from 5 to 15 annular atoms, wherein each ring contains 5 to 7 annular atoms and optionally one or more annular members is a heteroatom, , X^5 is $N(R^5)$, O or S, R^{10} is -OH, $-NHR^5$ or -SH and heteroatom n2, n3, n4, B, X^1, X^2, X^3, R^1, R^2, R^3, R^5 and R^4 are as defined above, to give a compound of Formula I in which X^4 and X^5 are adjacent members of an oxazol-2-yl, 1*H*-imidazol-2-yl or thiazol-2-yl ring; or

(b) reacting a compound of Formula 3:



3

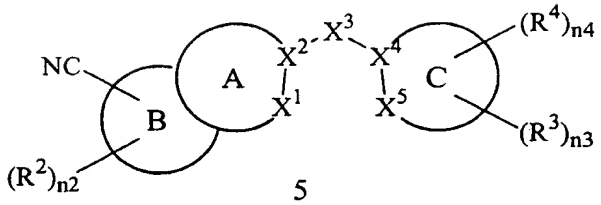
or a protected derivative thereof, with a compound of Formula 4:



4

or a protected derivative thereof, which R^9 is -C(O)L or -CN, wherein L is a leaving group, R^{10} is -OH, $-NHR^5$ or -SH and n2, n3, n3, B, C, X^3, X^4, X^5, R^1, R^2, R^3, R^4 and R^5 are as defined above, to give a compound of Formula I in which X^1 and X^2 are adjacent members of an oxazol-2-yl, 1*H*-imidazol-2-yl or thiazol-2-yl ring; or

(c) reacting a compound of Formula 5:



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with hydroxylamine hydrochloride, wherein n2, n3, n3, A, B, C, X^1, X^2, X^3, X^4, X^5, R^1, R^2, R^3 and R^4 are as defined above, to give a corresponding *N*-hydroxycarboxamidine and then dehydroxylating;

(e) optionally further reacting a compound of Formula I in which R^4, R^5 or R^7 comprises $-X^{13}C(O)OH$ with a compound having the formula $R^6X^{14}NHR^8$ to give a compound of Formula I in which R^4, R^5 or R^7 comprises $-X^{13}C(O)NR^8X^{14}R^6$, wherein X^{13} and X^{14} are linking groups containing n13 and n14 contiguous linking atoms, respectively, wherein the sum of n13 and n14 is 0 to 10, R^8 is hydrogen or (C_{1-6})alkyl and R^6 is as defined above;

(f) optionally further reacting a compound of Formula I in which R^4, R^5 or R^7 comprises $-X^{13}NHR^8$ with a compound having the formula $R^6X^{14}C(O)OH$ to give a compound of Formula I in which R^4, R^5 or R^7 comprises $-X^{13}NR^8C(O)X^{14}R^6$, wherein X^{13} and X^{14} are linking groups containing n13 and n14 contiguous linking atoms, respectively, wherein the sum of n13 and n14 is 0 to 10, R^8 is hydrogen or (C_{1-6})alkyl and R^6 is as defined above;

(g) optionally further reacting a compound of Formula I in which R^4, R^5 or R^7 comprises $-X^{13}NHR^8$ with a compound having the formula $R^6X^{14}S(O)_2Cl$ to give a compound of Formula I in which R^4, R^5 or R^7 comprises $-X^{13}NR^8S(O)_2X^{14}R^6$, wherein X^{13} and X^{14} are linking groups containing n13 and n14 contiguous linking atoms, respectively, wherein the sum of n13 and n14 is 0 to 10, R^8 is hydrogen or (C_{1-6})alkyl and R^6 is as above;

(h) optionally further reacting a compound of Formula I in which R^4, R^5 or R^7 comprises $-X^{13}NHR^8$ with a compound having the formula $R^6X^{14}C(O)H$ under reducing conditions to give a compound of Formula I in which R^4, R^5 or R^7 comprises $-X^{13}NR^8CH_2X^{14}R^6$, wherein X^{13} and X^{14} are linking groups containing n13 and n14 contiguous linking atoms, respectively, wherein the sum of n13 and n14 is 0 to 10, R^8 is hydrogen or (C_{1-6})alkyl and R^6

is as defined above;

(i) optionally converting a non-salt form of a compound of Formula I to a pharmaceutically acceptable salt with a pharmaceutically acceptable inorganic or organic acid or base;

(j) optionally converting an acid addition salt or base addition salt form of a compound of Formula I to the corresponding free base or free acid, respectively, with a suitable base or acid;

(k) optionally separating a mixture of stereoisomers of a compound of Formula I to give a single stereoisomer;

(l) optionally converting an unoxidized form of a compound of Formula I into a pharmaceutically acceptable *N*-oxide;

(m) optionally converting an *N*-oxide form of a compound of Formula I its unoxidized form;

(n) optionally converting a non-derivatized compound of Formula I into a pharmaceutically prodrug derivative; and

(o) optionally converting a prodrug derivative of a compound of Formula I to its non-derivatized form.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/25241

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D235/20 C07D403/14 C07D473/00 A61K31/415 C07D401/14
C07D401/06 C07D471/04 //(C07D471/04,235:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DE 28 39 989 A (HOECHST AG) 3 April 1980 see claims ---	1-11
Y	FAIRLEY T A ET AL: "STRUCTURE, DNA MINOR GROOVE BINDING, AND BASE PAIR SPECIFICITY OF ALKYL- AND ARYL-LINKED BIS(AMIDINOBENZIMIDAZOLES) AND BIS(AMIDINOBENZIMIDAZOLES) AND BIS(AMIDINOINDOLES)" JOURNAL OF MEDICINAL CHEMISTRY, vol. 36, no. 12, 1993, pages 1746-1753, XP002067234 see the whole document ---	1-11
Y	WO 95 19772 A (THE UNIVERSITY OF NORTH CAROLINA) 27 July 1995 see claims --- -/--	1-11

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 March 1999	18/03/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Henry, J

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 540 051 A (DAIICHI PHARMACEUTICL CO) 5 May 1993 see claims	1-11
Y	WO 95 08540 A (THE WELLCOME FOUNDATION LIMITED) 30 March 1995 see claims	1-11
Y	TIDWELL R -R ET AL: "DIARYLAMIDINE DERIVATIVES WITH ONE OR BOTH OF THE ARYL MOIETIES CONSISTING OF AN INDOLE OR INDOLE-LIKE RING. INHIBITORS OF ARGININE-SPECIFIC ESTEROPROTEASES" JOURNAL OF MEDICINAL CHEMISTRY, vol. 21, no. 7, 1 July 1978, pages 613-623, XP000573913 see the whole document	1-11
Y	CAUGHEY G H ET AL: "BIS(5-AMIDINO-2-BENZIMIDAZOLYL)METHANE AND RELATED AMIDINES. ARE POTENT, REVERSIBLE INHIBITORS OF MAST CELL TRYPTASES" JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 264, no. 2, 1993, pages 676-682, XP002064911 see the whole document	1-11
X	TIDWELL R.R. ET AL: "AROMATIC AMIDINES :COMPARISON OF THEIR ABILITY TO BLOCK RESPIRATORY SYNCYTIAL VIRUS INDUCED CELL FUSION AND TO INHIBIT PLASMIN,UROKINASE,THROMBIN,AND TRYPSIN" JOURNAL OF MEDICINAL CHEMISTRY., vol. 26, no. 2, 1983, pages 294-298, XP002094820 WASHINGTON US see the whole document	1-11
Y	CHEMICAL ABSTRACTS, vol. 89, no. 17, 23 October 1978 Columbus, Ohio, US; abstract no. 141219c, GERATZ J.D. ET AL: "SPECIFIC INHIBITION OF PLATELET AGGLUTINATION AND AGGREGATION BY AROMATIC AMIDINO COMPOUNDS" page 129; XP002094821 see abstract & THROMB. HAEMOSTASIS, vol. 39, no. 2, 1978, pages 411-425,	1-11

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/25241

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NAGAHARA T ET AL: "DIBASIC (AMIDINOARYL) PROPANOIC ACID DERIVATIVES AS NOVEL BLOOD COAGULATION FACTOR XA INHIBITORS" JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, no. 8, 15 April 1994, pages 1200-1207, XP000608128 see the whole document	1-11
P,X	WO 98 45275 A (AXYS PHARMACEUTICALS CORPORATION) 15 October 1998 see claims	1-11
P,X	WO 98 37075 A (BOEHRINGER INGELHEIM PHARMA KG) 27 August 1998 see claims	1-11
P,X	WO 98 01428 A (DU PONT MERCK PHARMACEUTICAL COMPANY) 15 January 1998 see claims	1-11

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/ 25241

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 10
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: not applicable
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: not applicable

In view of the extremely broad Markush claims,the search was executed with due regard to the PCT Search Guidelines(PCT/GL/2),C-III,paragraph2.1,2.3 read in conjunction with 3.7 and Rule 33.3 PCT,i.e. particular emphasis was put on the inventive concept,as illustrated by the compounds of claim 3 and particularly by the compounds of the examples
The international search was,in so far as possible and reasonable,complete in that it covered the entire subject-matter to which the claims are directed

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/25241

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 2839989 A	03-04-1980	AT 1285 T	15-07-1982
		AU 5082779 A	20-03-1980
		EP 0009163 A	02-04-1980
		JP 55040689 A	22-03-1980
		ZA 7904864 A	27-08-1980
WO 9519772 A	27-07-1995	AT 174508 T	15-01-1999
		AU 675386 B	30-01-1997
		AU 1679895 A	08-08-1995
		BR 9506552 A	28-10-1997
		CA 2179015 A	27-07-1995
		DE 69506686 D	28-01-1999
		EP 0739202 A	30-10-1996
		JP 9508369 T	26-08-1997
EP 0540051 A	05-05-1993	AT 136293 T	15-04-1996
		AU 666137 B	01-02-1996
		AU 2747092 A	06-05-1993
		CA 2081836 A	01-05-1993
		CN 1072677 A	02-06-1993
		CN 1168885 A	31-12-1997
		CN 1168886 A	31-12-1997
		CZ 284381 B	11-11-1998
		DE 69209615 D	09-05-1996
		DE 69209615 T	09-01-1997
		DK 540051 T	06-05-1996
		ES 2088073 T	01-08-1996
		FI 924932 A	01-05-1993
		GR 3019832 T	31-08-1996
		HR 921147 A	31-10-1995
		HU 65890 A	28-07-1994
		IL 103564 A	06-12-1998
		JP 10291931 A	04-11-1998
		JP 5208946 A	20-08-1993
		MX 9206295 A	01-08-1993
		NO 302948 B	11-05-1998
		NZ 244936 A	26-05-1995
		PL 170312 B	29-11-1996
		US 5576343 A	19-11-1996
		US 5620991 A	15-04-1997
		US 5866577 A	02-02-1999
		ZA 9208276 A	06-05-1993
WO 9508540 A	30-03-1995	AU 7661594 A	10-04-1995
		EP 0720603 A	10-07-1996
		HU 71345 A	28-11-1995
		JP 9506335 T	24-06-1997
		ZA 9407352 A	22-03-1996
WO 9845275 A	15-10-1998	AU 5895098 A	30-10-1998
WO 9837075 A	27-08-1998	DE 19706229 A	20-08-1998
		AU 6399198 A	09-09-1998
		HR 980082 A	31-10-1998
WO 9801428 A	15-01-1998	AU 3645697 A	02-02-1998